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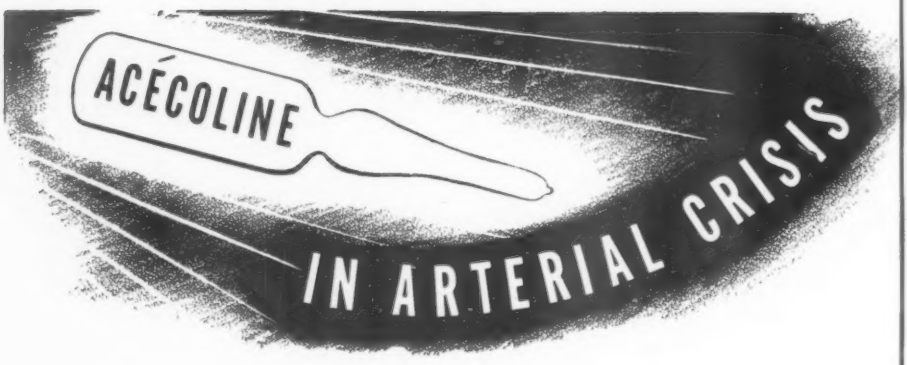

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THE AMERICAN JOURNAL
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NOVEMBER, 1945

ORIGINAL ARTICLES

HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS

EXPERIMENTAL STUDY OF IMMUNITY AND CROSS IMMUNITY IN VOLUNTEERS

A PRELIMINARY REPORT

BY CAPT. JOHN R. NEEFE, M.C., A.U.S.

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AND

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THE high incidence of infectious (epidemic) hepatitis and homologous serum hepatitis during the present war has stimulated extensive investigations of these two diseases. Unfortunately all attempts to isolate, identify and cultivate the causative agents have failed as have efforts to develop specific serologic or other tests and to find a susceptible animal. For these reasons, the relationship between homologous serum hepatitis and infectious (epidemic) hepatitis has remained obscure. Nevertheless, considerable information has been obtained. Certain similarities between the two diseases and their causative agents have been noted.[2,5,6,9] The causative agents of the two diseases both pass through bacteria trapping filters and survive heating at 56° C. for at least 30 minutes. They also produce similar clinical manifestations during the active disease and the pathologic changes apparently are the same. Both agents are present in the blood at some stages of the respective diseases. On the other hand, certain differences have been observed.[9,10] Infectious (epidemic) hepatitis usually, but not always, is associated with elevation of temperature above 100° F., whereas the temperature with homologous serum hepatitis usually does not exceed 100° (oral). In infectious hepatitis, the interval from exposure to jaundice usually is less than 40 days, whereas the interval from inoculation to jaundice in homologous serum hepatitis

usually is 60 or more days. Transmission of the causative agent to other persons by means other than injection of blood products is common from cases of infectious (epidemic) hepatitis but is rare from cases of homologous serum hepatitis. The causative agent of infectious hepatitis commonly is present in the feces of persons with this disease and produces the disease when administered by the oral route. However, the only reported attempt to transmit homologous serum hepatitis by the oral administration of feces from persons with this disease indicated that the agent either was not present in the feces or, if present, was not effective when administered by the gastro-intestinal route.[11]

The observations cited above, though suggestive of some difference in the causative agents of infectious hepatitis and homologous serum hepatitis, do not provide satisfactory evidence that the agents are different.

In order to obtain additional information on the relationship of these agents, a study of their antigenic properties, as indicated by immunity and cross immunity studies in human volunteers, was undertaken in 1943. Since that time, several papers dealing directly or indirectly with this subject have been published. A brief consideration of these data is pertinent to the present report.

Homologous Immunity in Infectious (Epidemic) Hepatitis. Cameron[1] has reported that second attacks (not relapses) of infectious hepatitis have been uncommon in Palestine where the disease is endemic. Findlay and his associates,[3] after a survey of 792 officers and 1822 enlisted men, came to the conclusion that one attack of infectious hepatitis probably produces considerable, but not absolute, immunity. Finally the infrequent occurrence of the disease in persons over 35 years of age, as compared with the relatively high incidence in children and young adults, suggests the former have acquired immunity from previous apparent or inapparent infections. To date, no adequate experimental study of homologous immunity following infectious hepatitis has been reported. However, the epidemiologic data suggest that one attack of infectious hepatitis is followed by some degree of homologous immunity.

Homologous Immunity in Homologous Serum Hepatitis. Apparently the only reported data on homologous immunity resulting from an attack of homologous serum hepatitis are those of Oliphant.[14] Twelve to 18 months after hepatitis produced by an agent in experimentally injected yellow fever vaccine (containing human serum) or in icterogenic human serum alone, 10 persons were reinjected with the yellow fever vaccine. At the same time, 10 apparently normal controls without history of previous hepatitis were injected with the same vaccine. Three of the 10 controls subsequently developed jaundice but none of those who previously had had serum hepatitis again developed the disease. These results suggest that the first attack of serum hepatitis was followed by immunity to the same hepatitis agent.

Cross-immunity Between Infectious Hepatitis and Homologous Serum Hepatitis. The reported data on cross-immunity are conflicting.

McFarlan and Chesney,[7] in the study of an army unit involved in an outbreak of homologous serum hepatitis following the prophylactic injection of a mumps convalescent plasma, found that 11 of the 175 injected men had a history of naturally occurring jaundice (probably infectious hepatitis) in childhood. Eight of these 11 men again developed jaundice following the injection of the mumps convalescent plasma. Thus the previous attack of naturally occurring jaundice did not protect against subsequent homologous serum hepatitis. In contrast, the epidemiologic investigations of Findlay and his associates[3] gave them the impression that persons who previously had had infectious hepatitis were less susceptible to serum hepatitis than normal persons. Their data, however, do not seem convincing. Concerning the occurrence of these two diseases in the reverse order, Gordon is quoted by Witts[11] as having observed that previous homologous serum hepatitis not only failed to protect against subsequent infectious hepatitis but may have increased the susceptibility to the latter disease. The data of Gordon were not described. On the other hand, the results of Oliphant's experimental study[14] suggested that homologous serum hepatitis was followed by immunity that also protected against an agent of infectious hepatitis. The ages of Oliphant's subjects were not mentioned, a factor which is of considerable importance in the interpretation of the results because of the decreased susceptibility of persons over 35 years of age to infectious hepatitis.

Protection by Human Immune Serum (Gamma) Globulin. The ability of human immune serum globulin to prevent or attenuate infectious (epidemic) hepatitis[4,15] indicates that large pools of human adult plasma may contain a protective substance which neutralizes or inactivates the causative agent. As human immune serum globulin is the fraction of blood plasma which contains specific antibodies for the causative agents of a variety of diseases, it is probable that the substance protecting against the agent of infectious hepatitis is a specific antibody present as a result of previous apparent or inapparent infection of the plasma donors. This globulin fraction contains many different antibodies and therefore might include antibodies for several hepatitis agents. For this reason, the protective properties of human immune serum globulin probably will not aid in solving the question of one or multiple causative agents of hepatitis.

The available immunologic data thus suggest that both infectious (epidemic) hepatitis and homologous serum hepatitis are followed by some degree of homologous immunity but the presence or absence of cross-immunity between the two diseases has not been established. Factors which may lead to erroneous interpretation of cross-immunity data and which may be responsible for the conflicting results reported to date include: (*a*) lack of knowledge of the sources of the hepatitis agents involved; (*b*) variation in susceptibility to infectious (epidemic) hepatitis with age; (*c*) uncertainty of the diagnosis or type of previous hepatitis based on history; (*d*) the probably frequent occurrence of unrecognized hepatitis without jaundice which may be followed by immunity; (*e*) the lack of knowledge of the presence of homologous

immunity in persons concerned in cross-immunity studies; (*f*) lack of knowledge concerning the duration of homologous immunity, assuming it exists. Although it is impossible to control all of these factors with the limited methods of study now available, an attempt has been made, in the present investigation, to eliminate as many of them as possible. Because the results to date have provided additional information, a preliminary report is presented at this time. The final results of this and related studies now in progress will be reported later.

Materials and Methods. In a previous report,[10] the data pertaining to the first stage of the experiment, namely, the basis for selection of volunteers, the initial experimental conditions, the methods of study, and the materials used for the experimental induction of homologous serum hepatitis, were fully described. After recovery from this disease, 6 of the subjects, ranging in age from 20 to 27 years, volunteered for tests of immunity and cross-immunity. With 1 exception, none of them had recognized hepatitis prior to participation in the first stage of the experiment. In 1939 while attending a university in Connecticut, subject H. J. C. had had a typical attack of "catarrhal jaundice," the onset occurring approximately 1 month after exposure to another student with this disease.

Subjects R. R. M. and C. R. L. first were inoculated* parenterally with plasma A,[10] a pooled mumps convalescent plasma known to contain a causative agent of homologous serum hepatitis. Subjects N. H. H. and J. C. first were inoculated with plasma B,[10] which was obtained from another volunteer 23 days after his inoculation with plasma A. Subjects S. B. E. and H. J. C. were inoculated first with a yellow fever vaccine[10] which also was known to contain a causative agent of homologous serum hepatitis. One of the donors, whose plasma was included in plasma A, previously had received an injection of one of the lots of yellow fever vaccine that had been followed by hepatitis in a number of recipients.[8] This donor developed hepatitis about 6 weeks after his plasma had been collected. It appears probable, therefore, that the same hepatitis agent was present in plasma A, plasma B, and the yellow fever vaccine. After recovery from hepatitis induced by parenteral administration of one of the 3 materials mentioned above, these 6 men were inoculated parenterally with plasma A (second inoculation; immunity test). After 190 to 218 days, they were inoculated (third inoculation; cross-immunity) with feces pool 1 FIH (1 subject, oral inoculation) or serum pool 2 SIH (5 subjects; parenteral inoculation). These materials, described elsewhere in detail,[12] contained a causative agent of infectious (epidemic) hepatitis that was responsible for an epidemic in a civilian summer camp located in Pennsylvania. 192 days after recovery from the hepatitis that followed his third inoculation, subject R. R. M. was reinoculated with feces pool 1 FIH. Sufficient time has not yet elapsed to carry out the final phase of this experiment, namely, reinoculation with the causative agent of infectious hepatitis, on the other 5 subjects.

At approximately the same time that the men received their second inoculations (plasma A; immunity test), 3 normal controls were inoculated parenterally with plasma A. In addition, 6 other normal persons who received this

* The term "inoculated" is used herein to indicate either oral or parenteral administration. The term "normal controls" is used to designate volunteers who had no previous history of hepatitis and had received no previous experimental inoculation with materials known to contain a hepatitis agent. The term "hepatitis with jaundice" is used to indicate hepatitis during which icterus was visible at some stage of the disease. Cases with clinical and laboratory evidence of hepatitis but without visible icterus have been designated as "hepatitis without jaundice." "Recovery" is used here to indicate absence of symptoms and physical signs and ability to return to usual duties.

plasma at other times also served as controls. At approximately the same time that those in the test group were inoculated parenterally with serum pool 2 SIH (third inoculation; cross-immunity), 3 normal controls were inoculated parenterally and 3 others were inoculated orally with this serum pool.

After each of the inoculations, the volunteers were observed carefully for symptoms and signs of any illness. Liver function studies were performed 2 or more times weekly.

Results. The results of the liver function studies and the approximate duration of symptoms following the three inoculations of the men tested for immunity and cross-immunity are shown in Figures 1 to 6. The results in these men and the controls are summarized in Table 1.

TABLE 1.—RESULTS OF IMMUNITY AND CROSS-IMMUNITY TESTS

	First inoculation			Second inoculation immunity test			Third inoculation cross-immunity test		
Subjects	Agent	Route	Hepatitis	Agent	Route	Hepatitis	Agent	Route	Hepatitis
R. R. M.	S.H. Plasma A	Par.	4+	S.H. Plasma A	Par.	0	I.H. Pool 1 FIH	Oral	3+
C. R. L.	S.H. Plasma A	Par.	4+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	3+
N. H. H.	S.H. Plasma B	Par.	2+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	2+
J. C.	S.H. Plasma B	Par.	1+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	2+
S. B. E.	S.H. Y.F.V.	Par.	3+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	1+
H. J. C.*	S.H. Y.F.V.	Par.	2+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	0
9 controls				S.H. Plasma A	Par.	8 (3 to 4+)			
12 controls							I.H.	6 Oral 6 Par.	5 (3 to 4+) 0

NOTE.—S.H., agent of homologous serum hepatitis; I.H., agent of infectious (epidemic) hepatitis; Par., parenteral; 0 indicates no evidence of hepatitis; ? indicates the occurrence of transient symptoms and/or laboratory findings suggestive of transient mild hepatic disturbance; 1+ indicates hepatitis without jaundice; characteristic symptoms associated with significant changes in hepatic function; 2+ indicates hepatitis without jaundice, the clinical and laboratory manifestations being more marked than those designated 1+; 3+ indicates hepatitis with overt jaundice; 4+ indicates hepatitis with overt jaundice, the manifestations being more marked than those designated as 3+.

* H. J. C. had infectious hepatitis 4 years prior to participation in these experiments.

Subject R. R. M. (Fig. 1.) (1) *First inoculation:* 75 days after he was injected parenterally with the serum hepatitis agent (plasma A, 12 ml.), he developed moderately severe hepatitis with jaundice. (2) *Second inoculation (immunity test)*: 154 days after the first inoculation and 34 days after recovery from the first attack of hepatitis, he again was injected parenterally with the same agent of serum hepatitis (plasma A, 10 ml.). No symptoms, physical signs, or laboratory evidence of hepatic disturbance were detected during the subsequent 194 days. (3) *Third inoculation (cross-immunity)*: 194 days after the second inoculation, he was inoculated orally with the causative agent of infectious (epidemic) hepatitis (feces pool 1 FIH, 5 ml.). After an incubation period of 25 days, he developed hepatitis with jaundice. (4) *Fourth inoculation* (not shown in Fig. 1): 270 days after the third inoculation and 192 days after recovery, he again was inoculated orally with the same agent of infectious hepatitis (feces pool 1 FIH). No evidences of hepatitis have been detected during the 100 days which have elapsed.

Subject C. R. L. (Fig. 2.) (1) *First inoculation:* approximately 100 days after his initial parenteral injection with the agent of serum hepatitis (plasma A,

9 ml.) he developed moderately severe hepatitis with jaundice. (2) *Second inoculation (immunity test)*: 223 days after the first inoculation and 85 days after recovery he again was injected parenterally with the same agent of serum hepatitis (plasma A, 5 ml.). Between the 57th and 61st days following the second injection, he experienced malaise, generalized aches and pains, mild anorexia and nausea, and 1 episode of vomiting. The symptoms were mild but were associated with a transient slight increase in bromsulphalein retention and slight increase in the excretion of urine urobilinogen. After the 61st day, he felt perfectly well and had no evidence of hepatic disturbance other than occasional weakly positive tests for bilirubin in the urine. (3) *Third inoculation (cross-immunity test)*: 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). After an incubation period of 28 days, he developed hepatitis with jaundice.

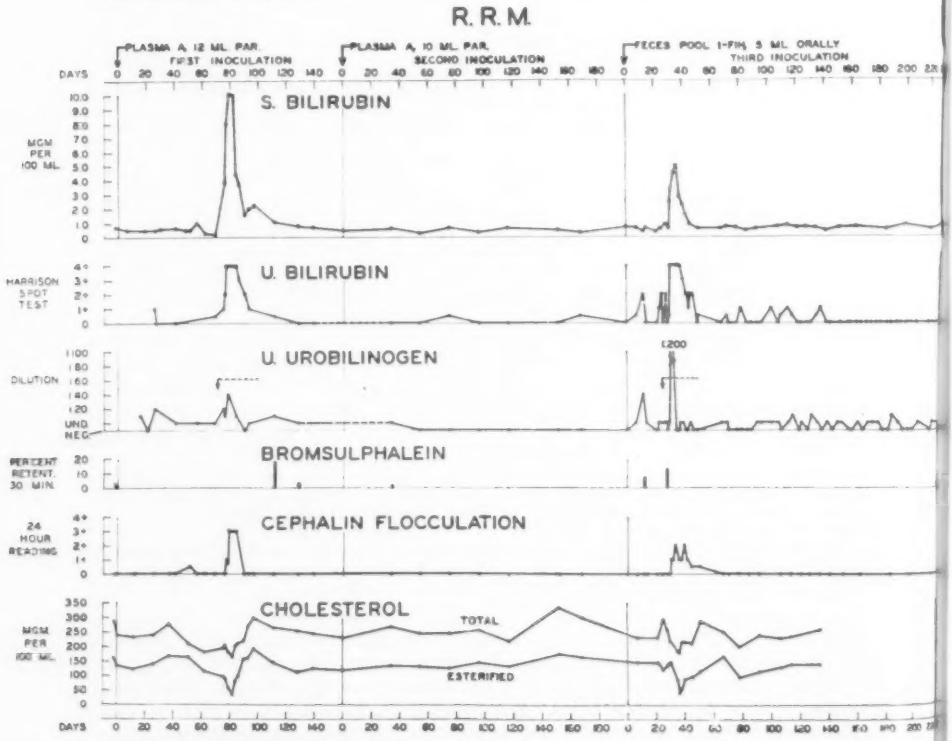

FIG. 1.—Laboratory data on R. R. M. in relation to the initial inoculation with a causative agent of serum hepatitis, the reinoculation with the same agent, and the subsequent inoculation with the causative agent of infectious hepatitis. Arrows and broken horizontal lines above the curve for urine urobilinogen indicate periods during which symptoms were present. "Par." indicates parenteral administration. Sections of curves for various tests shown by broken lines represent relatively long intervals during which no determinations were made. Readings between 0 and 1+ shown for the cephalin cholesterol flocculation test and the Harrison spot test for urine bilirubin indicate responses of questionable significance.

Subject N. H. H. (Fig. 3.) (1) *First inoculation:* from the 22nd to the 155th day after parenteral injection of an agent of homologous serum hepatitis (plasma B, 20 ml., probably containing the same agent as plasma A), he had laboratory evidence of mild hepatitis without jaundice. Malaise, anorexia

and nausea were present from the 23rd to the 26th day. After the 26th day, he felt perfectly well in spite of the continued positive laboratory evidence of hepatic disturbance. (2) *Second inoculation (immunity test)*: 240 days after the first inoculation and 85 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). Between the 83rd and 160th day after this injection, he had laboratory evidence suggestive of subclinical hepatic disturbance without jaundice. Malaise, weakness, easy fatigue, anorexia, nausea, vomiting and abdominal discomfort appeared on the 93rd day but these symptoms persisted for only 24 hours. After the 94th day he felt perfectly well. (3) *Third inoculation (cross-immunity test)*: 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). After an incubation period of 37 days, he developed typical symptoms and conclusive laboratory evidence of hepatitis without jaundice.

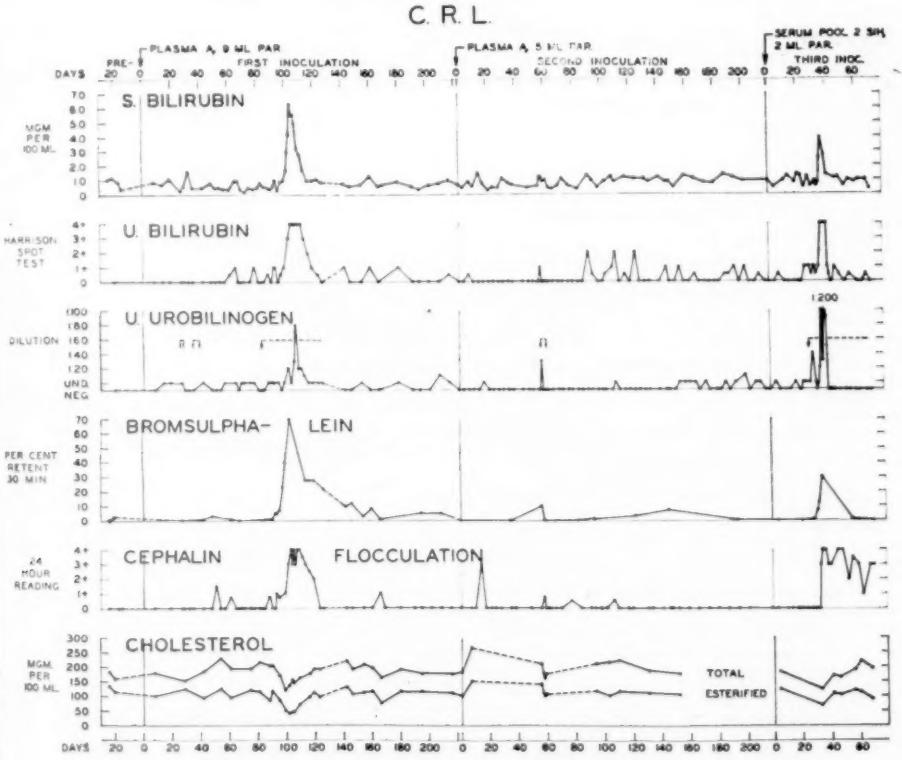

FIG. 2.—Laboratory and other data on subject C. R. L. (See Fig. 1 for legend.)

Subject J. C. (Fig. 4.) (1) *First inoculation:* from the 12th to the 62nd day after parenteral injection of the serum hepatitis agent (plasma B, 11 ml.), he had laboratory evidence of mild hepatitis without jaundice. Malaise, anorexia and nausea were present between the 12th and 14th and the 22nd to the 24th days. After the 24th day he felt perfectly well. (2) *Second inoculation (immunity test)*: 196 days after the first inoculation and 172 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). On the 141st day after this injection, he had malaise, and complained of weakness, easy fatigue, chilly sensations, pain in the back,

anorexia and abdominal discomfort. His temperature was elevated to 99.5° F. (oral). Most of the symptoms, which were associated with weakly positive tests for urine bilirubin, disappeared within 48 hours. No further symptoms or laboratory evidence of hepatic disturbance occurred after the 142nd day. (3) *Third inoculation* (*cross-immunity test*): 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). After an incubation period of 28 days he developed symptoms and conclusive laboratory evidence of hepatitis without jaundice.

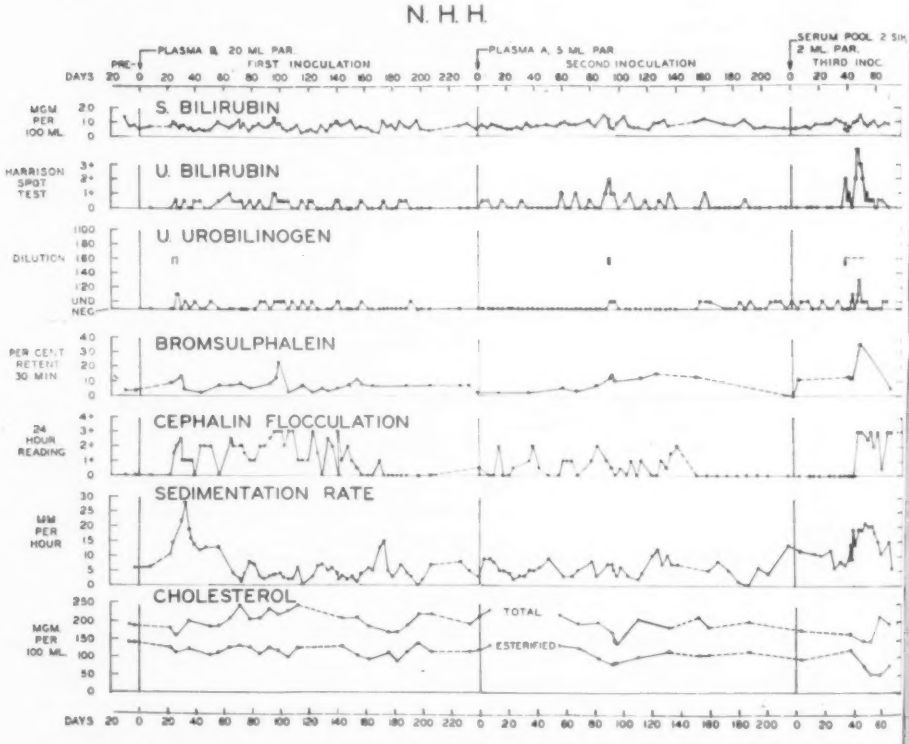

FIG. 3.—Laboratory and other data on subject N. H. H. (See Fig. 1 for legend.) Plasma B and plasma A presumably contained the same causative agent of homologous serum hepatitis.

Subject S. B. E. (Fig. 5.) (1) *First inoculation:* between the 75th and 150th day after parenteral injection with a serum hepatitis agent (yellow fever vaccine, 2 ml., probably containing the same agent as plasma A and B), he had symptoms and/or laboratory evidence of hepatitis. Jaundice was apparent from the 95th to the 107th day. (2) *Second inoculation* (*immunity test*): 254 days after the first inoculation and 104 days after complete recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). From the 38th to the 112th day after this injection, he had intermittent vague symptoms and/or laboratory findings suggestive of mild hepatic disturbance. The symptoms were mild and occurred intermittently in episodes of 24 to 48 hours duration. They included vague muscle pain, slight anorexia, mild nausea, excessive belching, vague abdominal discomfort and general malaise. The symptoms never were incapacitating. The laboratory findings included intermittently positive tests for urine bilirubin and elevation

of sedimentation rate without other obvious explanation. (3) *Third inoculation (cross-immunity test)*: 190 days after the second inoculation and 78 days after recovery, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). On the 35th day after his inoculation, he developed fever (100.2° F. oral), malaise, weakness, easy fatigue, joint, muscle, and back pain, headache, mild anorexia, excessive belching and abdominal discomfort. Some of these symptoms persisted intermittently until the 54th day. During this period, cephalin cholesterol flocculation tests gave significantly positive reactions but the other liver function studies showed no significant abnormalities.

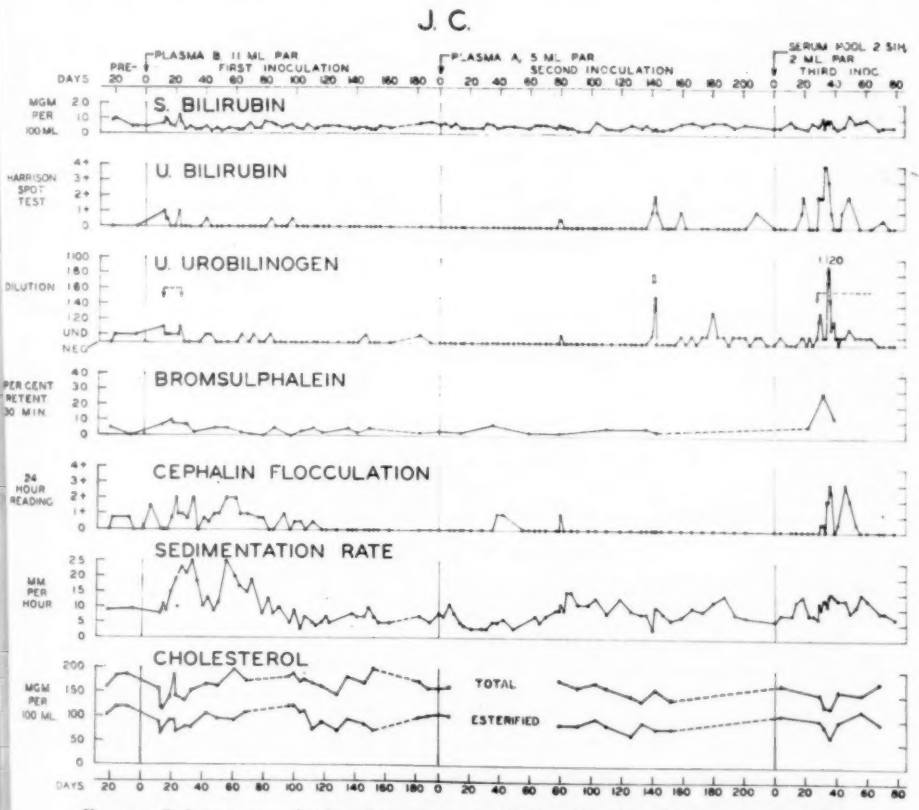

FIG. 4.—Laboratory and other data on subject J. C. (See legends of Figs. 1 and 3.)

Subject H. J. C. (Fig. 6.) As previously mentioned, this volunteer had naturally occurring catarrhal jaundice (probably infectious hepatitis) in 1939. (1) *First inoculation* (1943): on the 61st day after parenteral injection with the agent of serum hepatitis (yellow fever vaccine, 2 ml.) he developed hepatitis without jaundice. (2) *Second inoculation (immunity test)*: 226 days after the first inoculation and 125 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). During the subsequent 218 days, he had no definite symptoms although abnormalities in the results of the cephalin cholesterol flocculation test and the Harrison spot test for urine bilirubin were suggestive of subclinical hepatic disturbance. (3) *Third inoculation (cross-immunity)*: 218 days after the second inoculation he was injected parenterally with the agent of infectious hepatitis (serum pool

2 SIH, 2 ml.). During the 125 days which have elapsed to date, he has had no characteristic symptoms or laboratory evidences of hepatic disturbance.

Controls. The 3 normal controls inoculated parenterally with the serum hepatitis agent (plasma A, 5 ml.) at the time of the immunity tests all developed hepatitis with jaundice after 102, 103 and 108 days. Five of the 6 normal controls inoculated parenterally with this agent (plasma A; doses ranging from 1 to 250 ml.) at other times developed hepatitis with overt jaundice after 60 to 110 days (the one who failed to develop the disease received 100 ml. of plasma A).

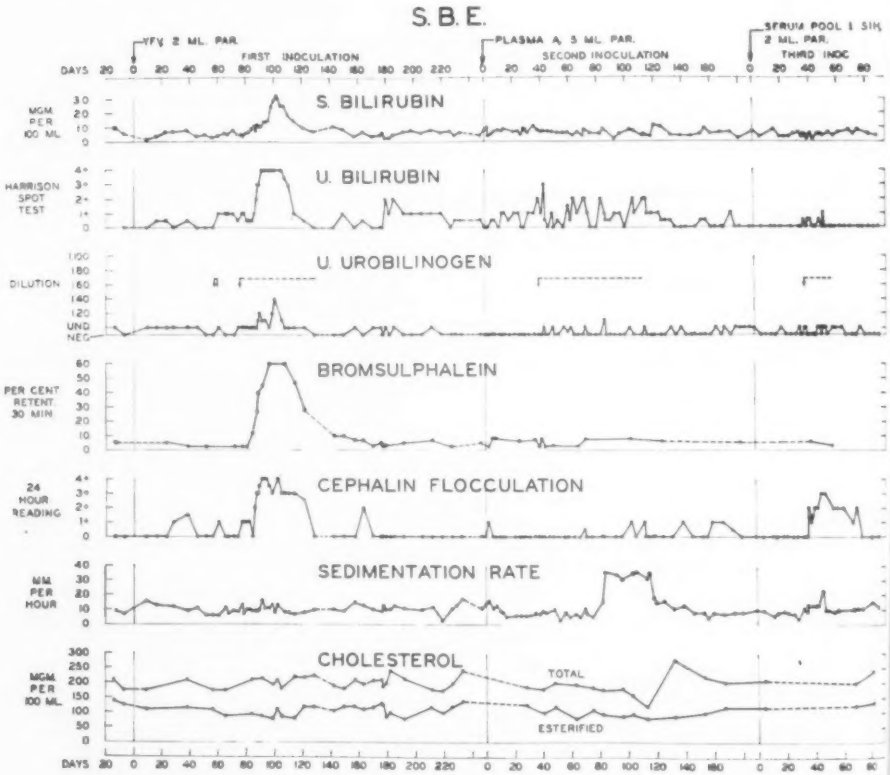

FIG. 5.—Laboratory and other data on subject S. B. E. (See Fig. 1 for legend.) The information available strongly suggests that the yellow fever vaccine and plasma A contained the same causative agent of homologous serum hepatitis (see text).

At the same time that 5 of the 6 men in the cross-immunity test group were inoculated parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.), 6 normal controls also were inoculated with this agent, 3 subjects receiving 2 ml. of serum pool 2 SIH parenterally and 3 receiving 3 ml. of this serum pool orally. None of the 3 controls inoculated parenterally has developed hepatitis during the 180 days elapsing to date whereas 2 of the 3 inoculated orally developed hepatitis with jaundice after incubation periods of 26 and 33 days. Similar results were obtained on oral and parenteral administration to normal controls of a Seitz filtrate of feces pool 1 FIH, which contained the same agent of infectious hepatitis as serum pool 2 SIH.[13] None of the 3 inoculated parenterally with the Seitz filtrate has developed hepatitis in the 180 days which have elapsed whereas all of the 3 inoculated

orally developed hepatitis with jaundice after incubation periods of 28, 30 and 32 days. Thus 5 of the 6 normal controls inoculated *orally* with materials containing this agent of infectious hepatitis developed the disease in contrast to none of the 6 inoculated *parenterally* with the same materials.

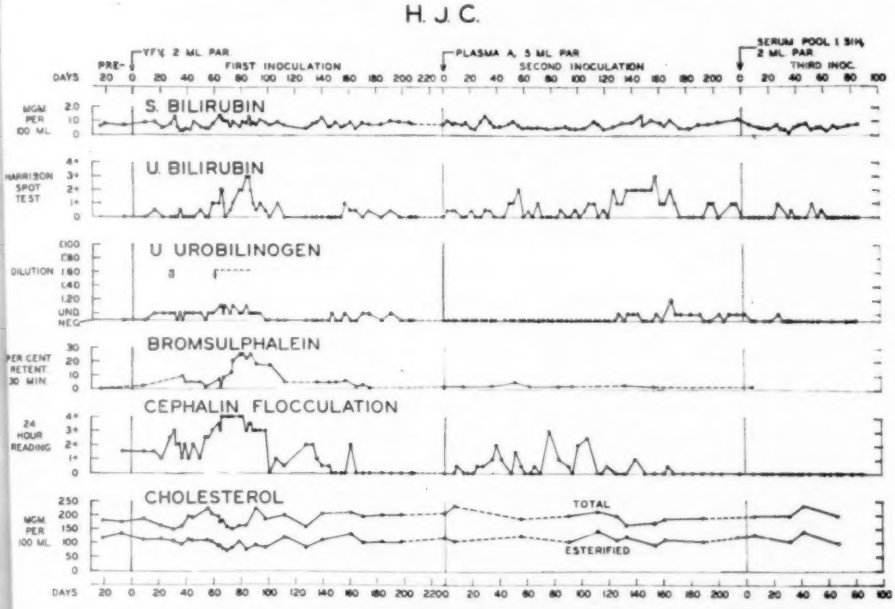

FIG. 6.—Laboratory and other data on subject H. J. C. (See legends of Figs. 1 and 5.) This subject had naturally occurring infectious hepatitis in 1939, 4 years prior to the first experimental inoculation.

Clinical Observations. In 11 of the 13 men (test group and controls) who developed hepatitis after inoculation with the serum hepatitis agent, the acute onset occurred after 60 or more days and none of the 13 men had elevations of temperature above 100° F. (oral). After oral or parenteral inoculation with the agent of infectious hepatitis, the longest incubation period in the 10 men (5 of the test group, 5 orally inoculated controls) contracting the disease was 37 days and all had elevations of oral temperature exceeding 100° F. at the onset.

Discussion. None of the 6 men who were inoculated with a causative agent of homologous serum hepatitis after recovery from homologous serum hepatitis developed incapacitating symptoms or jaundice. Although mild symptoms and/or laboratory findings suggestive of transient hepatic disturbance were observed in 5 of the 6 men, these manifestations were clinically insignificant and were not sufficient to establish definitely a diagnosis of hepatitis. On the other hand, 8 of the 9 normal controls inoculated with the same agent developed hepatitis with overt jaundice. Compared to the control subjects it is apparent that the men who previously had had homologous serum hepatitis were resistant to this causative agent of serum hepatitis.

The finding that the 6 men of the test group were resistant to the serum hepatitis agent in plasma A supports the presumption that

plasma A, plasma B and the yellow fever vaccine (see Material and Methods) contained the same hepatitis agent. The demonstration of resistance (immunity)* to the serum hepatitis agent also supports the diagnosis of the initial non-icteric illnesses of N. H. H., J. C. and H. J. C. as hepatitis without jaundice. The high susceptibility of the men in the control group to the serum hepatitis agent in plasma A provides evidence that the resistance of the test group to this agent resulted from their previous attacks of homologous serum hepatitis. For this reason the acquired resistance of N. H. H. and J. C. probably can be regarded as an illustration of the production of immunity by mild infection, which under ordinary circumstances, would not have been recognized as hepatitis.

Although resistant to the serum hepatitis agent, 5 of the 6 men again developed hepatitis after oral (1 man) or parenteral (5 men) inoculation with materials containing the causative agent of infectious hepatitis. Of the 5 men inoculated *parenterally* with such material, only 1 (H. J. C.) showed no subsequent evidence of hepatitis and he previously had had both infectious and homologous serum hepatitis. This is of importance because none of the 6 normal controls injected *parenterally* with this causative agent of infectious hepatitis developed the disease, a result which raises the question as to whether the hepatitis occurring in those who previously had had serum hepatitis was due to the agent of infectious hepatitis or to a reactivation of the serum hepatitis agent. Although reactivation of the serum hepatitis agent cannot be completely excluded, the following observations make this explanation improbable: (1) reactivation did not occur in Oliphant's series of inoculations 12 to 18 months after an attack of homologous serum hepatitis;[14] (2) the onset of hepatitis occurred 28 to 37 days after the inoculation, an interval corresponding to the incubation period of infectious hepatitis; (3) the subjects had been shown to be resistant to the agent of serum hepatitis and disappearance of this resistance during the interval between the immunity and cross-immunity tests seems improbable for the following reasons: (*a*) Oliphant's study of immunity[9] following homologous serum hepatitis indicated that the immunity persisted for at least 12 to 18 months. In the present investigation, the cross-immunity tests were completed within 12 months after the original attack of homologous serum hepatitis. Furthermore, during that 12 months, the men again had been inoculated with a serum hepatitis agent, a procedure which not only demonstrated their resistance to that agent but also might have maintained or even increased that resistance. (*b*) The only one of the test group who failed to show some evidence of hepatitis after inoculation with material containing the agent of infectious hepatitis previously had had both homologous serum hepatitis and infectious hepatitis, suggesting that he was protected by the previous attack of infectious hepatitis. The possibility that the serum hepatitis and infectious hepatitis agents were the same and that the last attacks of hepatitis

* The term "immunity" is used broadly throughout this report to indicate either complete or almost complete resistance to the hepatitis agent used.

were due to an overwhelming dose, sufficient to overcome the previously demonstrated resistance to the serum hepatitis agent, probably can be eliminated by the failure of the normal controls (injected parenterally) to develop the disease. The foregoing observations seem to justify the conclusion that the hepatitis which occurred in the men of the test group, following inoculation with materials containing the causative agent of infectious hepatitis, was not due to reactivation of the serum hepatitis agent, to reinfection with that agent after disappearance of the previously demonstrated resistance, or to breakdown of that resistance by an overwhelming dose of the same agent. For these reasons, it is probable that the last attacks of hepatitis in the men of the test group were due to the causative agent of infectious hepatitis which was known to be present in the serum with which they were inoculated (cross-immunity test). Thus it appears that these men were not protected against the agent of infectious hepatitis by their resistance to the agent of homologous serum hepatitis. The results strongly suggest a difference in the antigenic properties of the two agents employed. The difference may be explained either, on the basis of antigenic variation in strain of a single type of virus agent or an the basis of two different types of virus agent. Additional information may be provided by the challenge of volunteers shown to be immune to the causative agent of infectious hepatitis with the serum hepatitis agent, the reverse of the procedure employed in the present study. This type of cross immunity study will be conducted if volunteers continue to be available.

The experimentally induced infectious hepatitis in all cases was characterized by elevations of temperature greater than 100° F. at the onset and by an incubation period that did not exceed 37 days regardless of the route of inoculation (parenteral or oral). The experimentally induced homologous serum hepatitis was characterized by an interval of 60 or more days between inoculation and jaundice in 9 of the 11 cases and no elevations of temperature above 100° F. (oral) were observed. Although exceptions to the characteristic pattern have been noted, these differences are in accord with those described in the literature and they provide support for the immunologic evidence indicating some difference between the causative agents of the two types of hepatitis.

A difference in the causative agents employed herein also is suggested by the variation in results with different routes of inoculation. Thus *oral* administration of this agent of infectious hepatitis produced the disease in 5 of 6 normal persons whereas *parenteral* administration of the same agent failed to produce the disease in any of 6 other normal persons. On the other hand, *oral* administration of materials (plasma and feces) from patients with homologous serum hepatitis to a small group of normal persons has failed to induce the disease,[13] whereas *parenteral* administration of this serum hepatitis agent produced the disease in 8 of 9 normal persons. The experimental results with this causative agent of infectious hepatitis have suggested that normal persons are much more apt to develop the disease when the

agent is administered orally than when it is injected parenterally. In respect to this agent of homologous serum hepatitis, the preliminary studies have suggested that it is more apt to induce the disease in normal persons when injected parenterally than when administered orally. The results of additional experiments now in progress may confirm or modify these preliminary impressions.

The data also suggest that the ability of this causative agent of infectious hepatitis to induce the disease when injected parenterally may depend, in part, on previous infection by the serum hepatitis agent. Of the 10 persons without previous history of infectious hepatitis who were injected parenterally with this agent of infectious hepatitis, only the 4 who previously had had homologous serum hepatitis developed the disease. This strongly suggests that the persons who previously had had homologous serum hepatitis were more susceptible to the parenterally injected agent of infectious hepatitis than the controls with no previous history of homologous serum hepatitis.

Summary and Conclusions. Homologous serum hepatitis was induced experimentally in 6 human volunteers by the parenteral administration of materials known to contain a causative agent of this disease. After recovery, the 6 men were inoculated parenterally with a plasma that contained a causative agent of homologous serum hepatitis in order to test for homologous immunity. Nine normal control subjects without previous history of hepatitis also were inoculated parenterally with the same plasma. None of the 6 men in the test group developed incapacitating symptoms or jaundice, whereas 8 of the 9 controls developed hepatitis with jaundice.

The 6 men then were inoculated (1 orally, 5 parenterally) with materials known to contain a causative agent of infectious (epidemic) hepatitis in order to test for cross-immunity. Twelve normal controls without previous history of hepatitis also were inoculated with these materials, 6 receiving the infectious material orally and 6 receiving it parenterally. Of the 6 men tested for cross-immunity, 5 again developed hepatitis, the evidence being conclusive in 4 and very suggestive in the fifth person. The one who showed no evidence of hepatitis previously had had both infectious hepatitis and homologous serum hepatitis. None of the 6 normal controls inoculated parenterally developed hepatitis, whereas 5 of the 6 normal controls inoculated orally contracted typical infectious hepatitis.

The interval between inoculations with serum hepatitis agent and the onset of jaundice usually exceeded 60 days, whereas that between inoculation with the agent of infectious hepatitis and the onset of this disease did not exceed 37 days regardless of the route of inoculation. Oral temperatures did not exceed 100° F. in the cases due to the serum hepatitis agent, whereas the oral temperature exceeded 100° F., regardless of the route of inoculation, in all of the cases due to the agent of infectious hepatitis.

The groups employed in the studies reported herein are too small to warrant final conclusions regarding the relationship of the causative agents of infectious hepatitis and homologous serum hepatitis. Never-

theless the following observations provided considerable evidence that the two agents employed were not identical: (1) The susceptibility to the causative agent of infectious hepatitis of volunteers previously shown to be resistant to the causative agent of homologous serum hepatitis, suggesting a lack of cross-immunity, presumably due to a difference in the antigenic properties of the two agents. (2) The apparent difference in the ability of the two agents to produce hepatitis in normal persons when injected parenterally as indicated by (*a*) the occurrence of hepatitis in 8 of 9 normal persons who received the serum hepatitis agent parenterally, and (*b*) the failure of hepatitis to occur in any of 6 normal persons injected parenterally with the same causative agent of infectious hepatitis that produced the disease in 5 of 6 normal persons who received it orally.

Addendum. Since the preparation of this report for publication, Havens has reported an experimental study of immunity in hepatitis (Havens, W. P., Jr.: Experiment in Cross Immunity Between Infectious Hepatitis and Homologous Serum Jaundice, *Proc. Soc. Exp. Biol. and Med.*, **59**, 148, 1945). Three men who had recovered from experimentally induced homologous serum hepatitis were inoculated parenterally with an agent of infectious hepatitis. All developed hepatitis after incubation periods of 20 to 25 days. However, the existence of homologous immunity to the causative agent of homologous serum hepatitis was not determined in these men or in suitable controls so that no definite conclusions regarding cross immunity were drawn.

Since submission of this report for publication, 8 volunteers have been found to be resistant to reinfection by a causative agent of infectious (epidemic) hepatitis up to at least 8 months after recovery from previous hepatitis due to the same agent. Thus experimental evidence indicating the existence of homologous immunity following both infectious hepatitis and homologous serum hepatitis now is available. For this reason the susceptibility to the agent of infectious hepatitis of volunteers shown to be resistant to the agent of homologous serum hepatitis is best explained by a lack of cross immunity and by a difference, at least in their antigenic properties, in the two hepatitis agents studied.

This investigation was made possible by the coöperation of the administrative staffs of Selective Service (Camp Operations Division), the National Service Board for Religious Objectors, the American Friends Service Committee, the Philadelphia State Hospital, the New Jersey State Hospital, and we are particularly indebted to the members of Civilian Public Service Unit No. 140, Philadelphia, Penna., who volunteered as subjects in these investigations. The biochemical studies were supervised by Dr. John G. Reinhold, Principal Biochemist of the Philadelphia General Hospital.

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STREPTOMYCIN: ABSORPTION, DIFFUSION, EXCRETION AND TOXICITY*

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The antibiotic agent streptomycin was described by Schatz, Bugie and Waksman.[8] Several reports[1,3,4–7,10,11] have appeared which indicate that this substance may prove of value in treatment of infections caused by certain gram-negative, gram-positive and acid-fast bacteria. At the Mayo Clinic studies were begun in September, 1944, to explore the possible methods of administration and to obtain some information concerning absorption, diffusion, excretion and toxicity of the substance.

Streptomycin has been administered to human subjects by the continuous intravenous, intermittent intravenous, intermittent intramuscular, continuous intramuscular and intermittent subcutaneous routes. Streptomycin also has been administered intrathecally, by means of nebulization and orally. For determination of the concentration of streptomycin in various body fluids two methods have been employed. One method used was a modification of the Fleming slide cell technique described by one of us (D. H. H.).[2] The other method employed was a modification of the cup plate method of assay.[9] The test organism used in the cup plate method in determining concentration of streptomycin in the blood serum was a sensitive strain of *Staphylococcus aureus*. For determinations of the concentration of streptomycin in the urine, the test organism used was *Bacillus subtilis*. The present report deals with the results obtained in the studies just mentioned.

Absorption Following Various Methods of Administration. *Continuous Intravenous Drip.* On a theoretic basis, the continuous intravenous drip method of administration, which often has been used for administration of penicillin, appears to be the most satisfactory method of maintaining constant concentrations in the blood of patients who are

* The streptomycin used in these studies was kindly supplied, for the most part, by Dr. D. F. Robertson of Merck & Co., Inc. Small supplies of streptomycin also have been furnished by Abbott Laboratories, The Upjohn Company and Parke, Davis & Co. Some streptomycin, furthermore, was furnished by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

receiving streptomycin. Patients have received as much as 4,000,000 units of streptomycin per day by this method. The unit of potency, as originally described by the investigators at Rutgers University, was that quantity of the dry material which would inhibit the growth of a given strain of *Escherichia coli* in 1 cc. of nutrient broth or agar. It has been observed that the blood of a patient who was receiving 2,000,000 units of streptomycin per 24 hours by the intravenous drip method contained 31 units of streptomycin per cc., according to determinations made by the cup plate method. Likewise, the blood of a single patient who was receiving 1,000,000 units of streptomycin per 24 hours by this method contained between 6 and 8.7 units of streptomycin per cc.

Venous irritation at the site of injection has occurred at times; however, actual thrombosis rarely has been associated with this method of administration. Streptomycin of high potency is not seriously irritating for subcutaneous tissues and, therefore, significant discomfort will not result if the needle is accidentally displaced and the solution is forced into the subcutaneous tissues.

Intermittent Intravenous Administration. Although streptomycin may be administered intermittently by the intravenous route, intravenous administration has no advantages over intramuscular or subcutaneous injection. The concentration in the blood following a single intravenous injection is high for a short period but falls off more rapidly than when any other means of intermittent administration has been utilized (Tables 1 and 2). Discomfort has not occurred when as much as 100,000 to 200,000 units of streptomycin has been given in 10 to 20 cc. of physiologic saline solution. Single or repeated injections every 3 hours have been carried out by this method.

TABLE 1.—CONCENTRATIONS OF STREPTOMYCIN IN BLOOD SERUM FOLLOWING REPEATED INJECTIONS

Administration of streptomycin				Streptomycin in blood serum (units* per cc.)						
				Hours after first dose						
Case	Route	Dose every 3 hr. (units)	No. doses	1	3	6	9	12	Method of assay	Reactions
1	I.V.†	100,000	3	3 5.4	1.5 2.9	3 4.5	3 3.4	1.5 2.3	Slide cell Cup plate	None
2	I.V.	100,000	3	3 4.6	1.5 3	1.5 4	1.5 5.4	1.5 2.8	Slide cell Cup plate	None
3	I.M.†	100,000	3	1.5 2.7	1.5 2.6	1.5 2.6	1.5 3.3	0 1.2	Slide cell Cup plate	None
4	I.M.	100,000	3	1.5 3	1.5 3.3	3 4.5	3 4.3	1.5 2.8	Slide cell Cup plate	None
5	I.M.	400,000	3	3 3.6	3 2.1	6 11	3 3.9	3 2.3	Slide cell Cup plate	None
6	I.M.	400,000	3	3 5.7	3 2.8	3 5.8	3 6.9	0 2.6	Slide cell Cup plate	None
7	I.V.	400,000	3	14.5	14.9	13.2	7.5	4.1	Cup plate	Joint pain, fever, nausea, albuminuria, hematuria

* The units of potency used in these studies have been described elsewhere. Suffice to say here that the values obtained with their use were substantially equivalent to those obtained with the originally described *Escherichia coli* unit of the Rutgers investigators.

† I.V. = intravenous; I.M. = intramuscular.

TABLE 2.—CONCENTRATIONS OF STREPTOMYCIN IN BLOOD SERUM FOLLOWING SINGLE OR INTERMITTENT INJECTIONS

Case	Route of admin.	Amount per dose (units)	Streptomycin in blood serum (units per cc.) Hours after injection ½	1	2	3	4	Method of assay
1	I.V.	100,000	6	6	3	0	..	Slide cell
2	I.M.	100,000	3	3	3	3	..	Slide cell
3	Subcut.	100,000	3	3	3	1.5	..	Slide cell
4	Subcut.	200,000	6	6	6	6	..	Slide cell
			8.8	8.8	7.2	6.2	..	Cup plate
5	Subcut.	200,000	12.5	6	6	3	..	Slide cell
			10	7.7	6	..	..	Cup plate
6	Subcut.	200,000	12.5	25	6	6	..	Slide cell
7	Subcut.	100,000*	..	12.5	..	..	..	Slide cell
8	Subcut.	100,000*	..	12.5	25	6	..	Slide cell
9	Subcut.	115,000*	..	12.5	..	..	..	Slide cell
10	Subcut.	115,000*	..	6	..	..	..	Slide cell
11	Subcut.	150,000*	..	12.5	..	..	..	Slide cell
				16.6	..	..	..	Cup plate
12	Subcut.	250,000*	..	25	25	25	25	Slide cell
				31	24	16	10	Cup plate

* Dose indicated was administered every 3 hours.

Intermittent Intramuscular Administration. Under most clinical circumstances, probably intramuscular administration is the method of choice at present. Reasonable concentrations are maintained in the blood for at least 3 hours after administration, by this method, of adequate doses of streptomycin. In some instances, antibacterial amounts of streptomycin will be found to remain in the blood for as long as 4 to 6 hours after the last intramuscular injection has been made. For this method of administration the volume of solution which contains the streptomycin is kept at a minimum. Streptomycin of high potency can be administered by intramuscular injection; for instance, 100,000 units can be administered in 1 cc. of physiologic saline solution. The concentration of streptomycin in the blood following single and repeated intramuscular injections is recorded in parts of Tables 1 and 2. Intermittent intramuscular injection is made either into the gluteal or the deltoid muscles. A standard 22 gauge needle $2\frac{1}{2}$ inches (about 6.5 cm.) in length, usually is employed for making the injections.

Continuous Intramuscular Administration. A convenient method for continuous intramuscular administration of streptomycin is as follows: The contemplated daily dose of streptomycin is dissolved in 1 liter of saline solution and the intramuscular injection is made with the standard intramuscular needle. The rate of flow is regulated at approximately 8 to 10 drops per minute.

Intermittent Subcutaneous Administration. The subcutaneous method at times may prove satisfactory for repeated injections of streptomycin. Preparations of highest potency can be injected subcutaneously

every 3 hours, probably with less discomfort than when any other route of administration is used. Subcutaneous administration of relatively crude preparations at times may produce some pain and local irritation at the site of injection. Reasonably antibacterial amounts of streptomycin have been maintained in the blood of patients who have received streptomycin in amounts of 100,000 units every 3 hours subcutaneously (Table 2). One advantage of the subcutaneous method of administration is that highly trained personnel are not required. Student nurses as well as others can administer the material in this fashion. From limited studies it also appears that fairly purified streptomycin is less irritating than is penicillin to the subcutaneous tissues.

Intrathecal Administration. For reasons which will be mentioned later in connection with the diffusion of streptomycin, at times it may be necessary to administer the drug by the intrathecal route. Single injections of as much as 100,000 units of streptomycin, dissolved in 10 cc. of physiologic saline solution, have been administered intrathecally for meningitis. No evidence of serious untoward reactions has appeared. Antibacterial amounts of the substance have been found in the cerebrospinal fluid for at least 24 hours after these injections (Table 3). In 1 instance, detectable amounts of the substance were present in the cerebrospinal fluid for a considerably longer time.

TABLE 3.—STREPTOMYCIN IN CEREBROSPINAL FLUID

Case	Route of admin.	Dose (units)	Doses per day	Concentration in blood serum (units per cc.) Hours after injection ½	1	2	3	Concentration in cerebrospinal fluid (units per cc.) Hours after injection 2	3	12	26
1	Intrathecal	50,000	1	..	..	..	..	..	..	50	6
		100,000	1	..	..	..	..	..	..	6	
2	Subcut.	50,000	8	..	..	..	..	None detectable			
3	I.M.	60,000	8	..	1.5	1.5	1.5	0	0		
4	I.M.	60,000	8	..	3	3	1.5	0	0		
5	Subcut.	200,000	1	12.5	6	6	3	0	0		
6	Subcut.	200,000	1	6	6	6	6	0	0		

Administration by Nebulization. Experimentally, streptomycin in concentrations as high as 50,000 units per cc. was found to produce no irritation of the mucosa of the tracheobronchial tree. Three patients concerned in the present study received streptomycin by the tracheobronchial route. The material was administered by means of a nebulizer* connected to an oxygen tank equipped with reducing valve and flowmeter. As much as 500,000 units per day has been given, without interruption for periods as long as 4 weeks, for tuberculous involvement of the larynx and tracheobronchial tree. During the period of treatment, streptomycin was not demonstrable in the blood serum of the patients and excretion of streptomycin in the urine was negligible. In only 1 instance could streptomycin be detected in the urine of a patient who was receiving the agent by nebulization. This patient

* Vapo-efrin nebulizer.

was able to hold her breath for 5 seconds at the time of each inspiration, and she received 500,000 units of streptomycin in a period of 24 hours. The 24 hour urine specimen was found to contain 30,000 units of streptomycin. As was true of the other patients to whom the agent was administered by this method, streptomycin could not be detected in the blood serum.

Oral Administration. In connection with certain studies on the intestinal bacterial flora, a limited number of patients were given streptomycin by the oral route. One of us (F. R. H.) has found that striking reduction in the number of *E. coli*, as well as of other organisms present in the fecal stream, occurs when patients receive streptomycin orally. Studies indicate that streptomycin cannot be demonstrated in the blood serum when patients receive as much as 500,000 units of streptomycin per day by mouth. The substance was administered in doses of 125,000 units every 6 hours. Likewise, excretion of streptomycin in the urine of 1 such patient was negligible in a period of 24 hours. It appears, therefore, that streptomycin is not absorbed from the bowel when it is given in the manner described and when the total daily dose does not exceed that named. Knowledge of whether or not absorption will occur following administration of larger doses of streptomycin must await further studies.

Diffusion and Excretion. *Diffusion Into Cerebrospinal Fluid.* It was considered of importance to determine whether or not diffusion of streptomycin into the cerebrospinal fluid takes place. Intramuscular and subcutaneous injections of varying amounts of streptomycin have been administered to human beings. The largest single dose administered in this study was 200,000 units. Concentrations in the blood serum and in the cerebrospinal fluid were determined at various intervals following the injections. In some cases, determinations were carried out on blood serum collected $\frac{1}{2}$, 1, 2 and 3 hours after the injection. It is evident, from examination of the data given in Table 3, that antibacterial amounts were present in the blood of these patients during this entire period. Detectable amounts of streptomycin were not found in cerebrospinal fluid removed 2 and 3 hours after injection. It would appear, therefore, that diffusion of streptomycin into the cerebrospinal fluid, when given in the amounts stated, does not take place readily. On the other hand, large doses given intramuscularly, subcutaneously or intravenously, in the presence of meningitis, have resulted in diffusion into the cerebrospinal fluid, to yield concentrations therein approximating one-fifth that in the blood serum of the same patients.

Diffusion Through the Placenta (Placental Transmission). It was considered desirable to determine whether or not streptomycin, when present in the blood of the mother, passed the placental barrier and was, therefore, present in the fetal circulation. In this study varying amounts of streptomycin were administered before the time of delivery. The interval of time between the last dose and the time of delivery varied from 45 minutes to 2 hours and 35 minutes. In some instances,

single injections of streptomycin were carried out and in some instances it was possible to give repeated injections before the time of delivery. Blood was obtained from the mother at the time of delivery and specimens of blood from the umbilical cord were obtained simultaneously. It is evident, from examination of Table 4, that streptomycin traverses the placenta and is readily available in the fetal circulation. The concentration of streptomycin in the blood of the umbilical cord appears to vary somewhat, depending on the dose and the time which elapses between the last injection and birth.

TABLE 4.—PLACENTAL TRANSMISSION OF STREPTOMYCIN

Case	Route of admin.	Dose (units)	No. doses	Delivery (time after dose)	Concentration in blood (units per cc.)		Method of assay
					Maternal	Cord	
1	Subcut.	100,000	1	1 hr. 30 min.	6.0	1.5	Slide cell
2	Subcut.	100,000	1	2 hr. 35 min.	3.0	3.0	Slide cell
3	Subcut.	100,000	7*	45 min.	12.5	12.5	Slide cell
4	Subcut.	100,000	7*	1 hr. 30 min.	6.0 10.5	6.0 6.4	Slide cell Cup plate

* Administered every 2 hours.

Excretion of Streptomycin in Bile. Studies on the excretion of streptomycin in bile are incomplete but are sufficient to indicate that the material apparently is concentrated and excreted in the bile. The results of observations on excretion of streptomycin in bile are shown in Table 5. The patient received 100,000 units of streptomycin subcutaneously every 3 hours for 5 days. Two hours after the first injection of 100,000 units of streptomycin, the blood serum contained 6 units of streptomycin per cc. At this time, the concentration of streptomycin in the bile was 12.5 units per cc. The concentrations in the bile, on the 2nd and 3rd days of administration of streptomycin, were between 3 and 6 units of streptomycin per cc.

TABLE 5.—EXCRETION OF STREPTOMYCIN IN BILE*

Administration of streptomycin							
Route	Dose every 3 hr. (units)	Doses per day	Day	Hour after first dose	Concentration in blood serum (units per cc.)	Concentration in bile (units per cc.)	Total 24-hr. output in bile (units)
Subcut.	100,000	8	1	2 4	6 6	12.5 12.5	
Subcut.	100,000	8	2	..	..	6	2010
Subcut.	100,000	8	3	..	..	3	960

* Determinations of streptomycin in the bile were made by means of the slide cell method of assay

Determination of the quantity of bile and of bile salts excreted in 24 hours is said to be a reliable test of liver function. It is evident, from examination of Table 6, that no serious alteration occurred in either of these values during the period when the patient just referred to was receiving 800,000 units of streptomycin per 24 hours. It should be emphasized that these data do not permit conclusions as to

the possible effect of streptomycin on liver function following long periods of administration of the preparation.

TABLE 6.—EFFECT OF STREPTOMYCIN ON VOLUME OF BILE AND WEIGHT OF BILE SALTS EXCRETED*

Day	Dose of streptomycin per 24 hr. (units)	Bile (cc.)	Bile salts per 24 hr., (gm.)
1	800,000	250	11.25
2	800,000	250	11.68
3	800,000	285	9.69
4	800,000	255	9.51
5	800,000	315	11.84

* This is the same case as that represented in Table 5.

Excretion of Streptomycin in Urine. It is evident that following systemic administration of streptomycin, fairly large amounts of the material are absorbed into the general circulation and excreted in the urine. From one-half to three-fourths of the total amount of streptomycin administered is usually excreted in the urine during the 1st 24 hours. High concentrations (as much as 434 units per cc.) may on occasion be found in the urine of patients who have received large amounts of the material (Table 7). It should be emphasized here that the cup plate method is the technique of choice for determining the presence of streptomycin in the urine.

TABLE 7.—URINARY EXCRETION OF STREPTOMYCIN*

Case	Route of admin.	Dose every 3 hr. (units)	Doses	Urine	Streptomycin (units per cc. of urine)	Total urine excreted (cc.)	% streptomycin excreted
1	I.V.	100,000	3	1st 24 hr.	120	2000	80.0
2	I.V.	100,000	3	1st 24 hr.	126	1245	52.3
3	I.M.	100,000	3	1st 24 hr.	104	1665	57.4
				2nd 24 hr.	7.2	725	1.7
4	I.M.	100,000	3	1st 24 hr.	78.4	2510	65.6
				2nd 24 hr.	5.6	1350	2.5
5	I.M.	400,000	3	1st 24 hr.	137	1850	21.1
				2nd 24 hr.	6.1	2150	1.1
6	I.M.	400,000	3	1st 24 hr.	137	1460	16.7
7	I.V.	400,000	3	1st 24 hr.	434	1740	62.9

* The cup plate method of assay was used. These are the same 7 cases as those represented in Table 1.

Consideration of Toxicity. *Irritation at the Site of Injection.* It has been pointed out that local irritation may occur occasionally following administration of streptomycin by the intravenous drip method. Actual thrombosis rarely has occurred; however, often it is necessary to change the site of injection frequently. Pain at the site of subcutaneous or intramuscular injection also may occur, especially when streptomycin of low potency is used. The discomfort is described as a burning sensation and usually is of short duration. Neither of these reactions has been troublesome, nor do the reactions seriously interfere with administration of the agent. It is exceedingly important

that the size of the inoculum be kept as small as possible (no more than 2 or 3 cc.).

Chills and Fever. On occasions, chills and fever have occurred following administration of streptomycin. This reaction is not unlike reactions encountered in the past in connection with administration of penicillin which was not pyrogen-free. More frequently a slight elevation of temperature is noted, which is usually not of serious significance.

Cutaneous Toxic Manifestations. At times generalized flushing, not unlike that seen in association with a histamine reaction, has been observed in cases in which relatively impure streptomycin has been administered. Likewise, dermatitis (toxic erythema) and cutaneous eruptions of an urticarial type have occurred following administration of streptomycin as it is available at present for clinical use. Although administration of streptomycin may be continued in the presence of these cutaneous eruptions, it is exceedingly important to remember that severe dermatitis may result.

Joint Pain. Several patients who received streptomycin complained of severe pain in the joints and muscles of the extremities. Such patients usually exhibited fever and other evidences of intolerance for the substance.

Nausea. A few patients who received streptomycin, and who exhibited one or more of the aforementioned reactions, complained of nausea and, on occasions, they had vomited.

Effects on Renal Function. All patients who received streptomycin were carefully studied with regard to possible impairment of renal function. Determinations of blood urea have been made frequently on all patients who have received the substance. In no instance has there been any evidence of rising concentrations of blood urea. Likewise, in some instances, urea clearance tests have failed to reveal any significant change; in fact, as much as 150,000,000 units of fairly potent streptomycin has been administered, over a period of 42 days, to a single patient who had solitary kidney (average daily dose approximately 3,500,000 units) without evidence of interference with renal function.

On the other hand, repeated large doses of streptomycin at times have been followed by evidence of renal irritation. For example, in Case 7 (Table 1) the patient received 400,000 units of streptomycin intravenously every 3 hours for 3 doses. Albuminuria and microscopic hematuria developed; however, no evidence of permanent renal damage followed cessation of administration of the substance. This amount (3,200,000 units per day) is in excess of the average contemplated daily therapeutic dose.

Effect on Liver Function. As was suggested in an earlier paragraph, at the time this report was written, no conclusive evidence had been presented of interference with hepatic function following the use of streptomycin in amounts reported in this paper.

Effect on the Hemolytopoietic System. In all cases concerned in the present report, determinations of the hemoglobin content of the blood

were made frequently and erythrocyte, leukocyte and differential blood counts were made before, during and after administration of streptomycin. Likewise, blood smears were examined frequently for evidence of any morphologic change after short or prolonged treatment with streptomycin. In no instance has any effect been noted which could be attributed to the preparation.

Summary. The antibiotic substance, streptomycin, has been administered to a number of human beings in amounts which could, on a theoretic basis, be regarded as therapeutically effective. The number of patients concerned in the study is only partially represented by the 30 patients accounted for in the tables which accompany the paper. Approximately 10 others are referred to in the text. The material can be administered intravenously, intramuscularly or subcutaneously. The substance also can be administered by the intrathecal route, by nebulization or by the oral route. It would appear that if intermittent methods of parenteral administration are to be used, the substance should be administered at least every 3 or 4 hours in a manner similar to that which has been employed for administration of another antibiotic agent, penicillin.

It appears that diffusion of streptomycin into the cerebrospinal fluid does not readily take place unless large doses are administered. On the other hand, following parenteral administration, streptomycin is readily absorbed into the general circulation and is excreted for the most part in the urine. From the studies reported herein, it appears that diffusion of streptomycin through the placenta takes place and that streptomycin is available in the fetal circulation. Streptomycin also appears to be concentrated and excreted in the bile.

Serious and uncontrollable toxic reactions have not been encountered following administration of fairly large amounts of streptomycin in single or repeated injections. In some instances, streptomycin has been administered to patients for a considerable time without evidence of toxic reactions.

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THE ANTAGONISM OF LOCAL ANESTHETICS AGAINST THE SULFONAMIDES

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The inhibition of the antibacterial action of the sulfonamide drugs by procaine ("novocaine"), the most widely used of the local anesthetics, has been clearly demonstrated by Peterson and Finland,[8] who summarized the earlier literature in their report. Procaine, an ester of p-aminobenzoic acid, can be hydrolyzed, with liberation of free p-aminobenzoic acid, by esterases present in human tissues.[6] Thus the mechanism of inhibition of sulfonamides by procaine can be attributed to its structural similarity to a "natural" antagonist, p-aminobenzoic acid, and in all probability to the p-aminobenzoic acid actually formed by hydrolysis of procaine.

Keltch, Baker, Krahl and Clowes[2] found that 5 other esters of p-aminobenzoic acid which had local anesthetic properties were inhibitory to sulfonamide bacteriostasis. The same authors reported that another group of local anesthetics which were not esters of p-aminobenzoic acid or of substituted p-aminobenzoic acids, had no inhibitory effect. Winkler[9] similarly found inhibition by 3 esters of p-aminobenzoic acid, and no inhibition by a local anesthetic which was a quinoline derivative with no p-aminobenzoyl group.

At the request of Dr. C. W. Sondern, of the White Laboratories, Inc., certain substances with proved or putative local anesthetic action were studied by us with regard to their activity as sulfonamide-antagonists. Other substances, including many of those reported by the above-mentioned authors, were simultaneously investigated to serve as controls. The present report deals with these local anesthetics and other substances. We have repeated, in most cases confirmed, and in some cases extended the work of other investigators, and in addition presented data on a few substances not previously studied.

M-aminobenzenesulfonamide has no activity against microörganisms comparable to that of sulfanilamide. This is in accordance with a hypothesis proposed by Kumler and Halverstadt[3] based upon the possible existence of resonance isomers of sulfanilamide which are impossible with the meta configuration. On purely theoretical grounds it would not be expected that either o-aminobenzoic acid or m-aminobenzoic acid would act in a manner comparable with p-aminobenzoic acid in regard to inhibition of the sulfonamides. Landy and Wyeno[4] reported no antisulfanilamide action demonstrable with either the

ortho or the meta isomer. Benigno,[1] however, is reported in an abstract of a paper published in 1943 to have stated that the actions of o- and m-aminobenzoic acids are similar to that of p-aminobenzoic acid but much weaker. Therefore, these substances, and certain local anesthetics derived from one of them, were consequently included in our study.

Methods of Investigation. Our procedure was based upon the method used by Peterson and Finland.[8] Sulfathiazole (0.2 ml. of 0.002 molar solution) was mixed with equine blood (0.5 ml.) and a suspension (0.1 ml.) of a known number of organisms (hemolytic streptococcus, N.Y.5 strain, or in a few experiments pneumococcus Type III). To this was added the local anesthetic or other drug under investigation in known molar concentration and in a volume of 0.1 ml. Under these conditions the molar ratio[7] of sulfathiazole to "inhibitor" could easily be calculated.

The only unmeasured variable in this system was the amount of inhibiting substances in the blood. To control this doubtful factor, each experimental run was accompanied by control runs, using an equal number of tubes containing blood and organisms alone, and an equal number containing blood, organisms, and sulfathiazole. Volumes were kept consistently at 0.9 ml. total by the addition of sterile saline solution. Blood was used in all experiments, again following the example of Peterson and Finland,[8] since its presence provides a closer approximation to conditions *in vivo*, and since it serves as a quick indicator of bacterial growth. Incubation was carried on for 48-hour periods at 37° C., with mechanical rocking replacing the rotating drum of Peterson and Finland. Because of mechanical difficulties, all experiments were not rocked for the full time. No changes in results could be attributed to this change in technique. All negative or doubtful tubes were subcultured. Organisms were grown and diluted in tryptic digest broth.

A typical experiment is shown in Table 1. The significant observations to

TABLE 1.—RESULTS OF A TYPICAL EXPERIMENT SHOWING MINIMAL INOCULUM SURVIVING WITH SULFATHIAZOLE ALONE AND WITH AN INHIBITING AND NON-INHIBITING LOCAL ANESTHETIC

	Logarithm of total initial number of organisms (hemolytic streptococci, N.Y.5 strain)					
	6	5	4	3	2	1
Control	+	+	+	+	0	0
Sulfathiazole, 4.4×10^{-4} M.	+	+	0	0	0	0
Sulfathiazole plus procaine-HCl, 1.1×10^{-3} M.*	+	+	+	+	+	0
Sulfathiazole plus procaine-HCl, 1.1×10^{-1} M.†	+	+	+	+	0	0
Sulfathiazole plus benzyl alcohol, 1.1×10^{-3} M.*	+	+	0	0	0	0
Sulfathiazole plus benzyl alcohol, 1.1×10^{-4} M.†	+	+	0	0	0	0

+ = growth in 48-hour subculture. 0 = 48-hour subculture sterile.
* Molar ratio, 0.4.
† Molar ratio, 4.

be made are: (1) the logarithm of the number of organisms in the smallest inoculum (log MVI) surviving in the control tubes, which contain blood and broth alone; (2) the logarithm of the minimal viable inoculum in the tubes containing sulfathiazole in addition to blood and broth; and (3) the logarithm of the minimal viable inoculum in experimental tubes containing blood and broth, sulfathiazole and the substance under test for inhibiting effect. The difference (2) minus (3) gives us the logarithm of the ratio MVI for sulfathiazole/MVI for sulfathiazole plus inhibitor. The magnitude of this difference is a rough measure of inhibitory action and may be considered an "index of inhibition." If this is positive, it indicates inhibition; if it is zero, it indicates no effect; if it is negative, it indicates additional bacteriostatic or bactericidal effect.

Results. In several experiments the inhibitory action of procaine was compared with that of p-aminobenzoic acid. If concentrations are figured in terms of molarity, there is no quantitative difference between the inhibitory effect of the free acid and of the ester. A typical experiment is shown in Table 2.

TABLE 2.—RESULTS OF A TYPICAL EXPERIMENT SHOWING AGREEMENT IN INHIBITORY EFFECT BETWEEN EQUIMOLAR CONCENTRATIONS OF PROCAINE AND OF P-AMINOBENZOIC ACID

	Logarithm of total initial number of organisms (pneumococci Type III)					
	6.1	5.1	4.1	3.1	2.1	1.1
Control	+	+	+	+	+	0
Sulfathiazole, 4.4×10^{-4} M.	+	+	+	0	0	0
Sulfathiazole plus p-aminobenzoic acid, 1.1×10^{-5} M.*	+	+	+	+	+	0
Sulfathiazole plus procaine-HCl, 1.1×10^{-5} M.*	+	+	+	+	+	0

* Molar ratio, 40.

The experiment in Table 2 and a few preliminary experiments were done with Type III pneumococcus as the test organism, following the example of Peterson and Finland.[8] For the main experimental series Group A hemolytic streptococcus became the organism of choice, since it offered fewer cultural difficulties. All experiments with hemolytic streptococci are summarized in Table 3.

TABLE 3.—INDICES OF INHIBITION OF ALL SUBSTANCES TESTED AGAINST SULFATHIAZOLE USING HEMOLYTIC STREPTOCOCCUS, N.Y.5 STRAIN, AS TEST ORGANISM

Substance	Molar ratio (sulfathiazole/inhibitor)			
	400	40	4	0.4
p-aminobenzoic acid*	1	2		
Procaine*	..	2	2	3
o-aminobenzoic acid*	..	..	0	0
m-aminobenzoic acid*	..	..	0	0
Orthoform	..	..	0	0
3-amino-4-hydroxypropylbenzoate	..	0	0	0
3-amino-4-hydroxybenzoic acid	..	..	0	0
Alypin*	..	0	0	0
Apothesine*	..	0	0	0
Benzyl alcohol	..	0	0	0
Cocaine*	..	0	0	0
Diothane*	..	0	0	−1
Metycaine*	..	0	0	0
Nupercaine*	..	−1	−1	−1
Phenacaine*	..	−1	−1	−1
Tetracaine*	..	0	0	0

* The starred substances have been previously studied and reported by other investigators. They are included here in agreement with the previous reports.[2,4,5,8]

The results outlined in Table 3 confirm the results of previous investigators in the following respects: (1) p-aminobenzoic acid and its ester procaine show definite evidence of inhibition; (2) local anesthetics which are not esters of p-aminobenzoic acid show no such inhibition; (3) tetracaine, an ester of p-butylaminobenzoic, shows no inhibition.

Benigno,[1] in an article which we have seen only in abstract, claims a weak antisulfonamide action for o- and m-aminobenzoic acid. This is not confirmed by our work. Three derivatives of m-aminobenzoic

acid (orthoform N.N.R., which is 3-amino-4-hydroxymethylbenzoate, also 3-amino-4-hydroxypropylbenzoate, and 3-amino-4-hydroxybenzoic acid) were also found to be without inhibitory action against sulfathiazole.

Certain of the local anesthetics studied show not only no inhibitory effect against the sulfonamide, but an actual additional antibacterial effect. This was true of nupercaine and phenacaine, and to a less degree of diothane.

Summary. 1. The inhibitory effect of procaine has been found exactly comparable, mol for mol, with that of p-aminobenzoic acid upon sulfathiazole.

2. 0-aminobenzoic acid and m-aminobenzoic acid are without inhibitory effect upon sulfathiazole.

3. Three derivatives of m-aminobenzoic acid (3-amino-4-hydroxymethylbenzoate (orthoform, N.N.R.), 3-amino-4-hydroxypropylbenzoate, and 3-amino-4-hydroxybenzoic acid) are likewise without inhibitory effect.

4. The work of previous investigators demonstrating no antisulfonamide action of local anesthetics other than the derivatives of p-aminobenzoic acid is confirmed.

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THE PENETRATION OF PENICILLIN INTO JOINT FLUID FOLLOWING INTRAMUSCULAR ADMINISTRATION

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Penicillin administered to man by the intramuscular, intravenous or subcutaneous routes has been shown to appear rapidly in the blood serum, to appear in the bile in higher concentrations than in the serum and to be excreted in the urine.[1,11,12] It is not found in detectable amounts in the saliva, nor in the normal spinal fluid,[11] but is present in the spinal fluid when the meninges are inflamed.[5] Penicillin has been detected in low concentration in the red cells,[11] lachrymal secretions,[11] and even to a minimal extent throughout the tissues of the

eyeball excepting the ocular lens.[15,16] Earlier studies[1,11] have not clarified the extent to which penicillin is transferred to the synovial fluid. This has resulted in some doubt as to whether following systemic administration a sufficient amount of penicillin would reach the joint fluid to be effective in the treatment of the purulent arthritides. However, clinical observations by both Herrell[8,9] and by Dawson[6] indicate that effective antibacterial amounts of penicillin may be obtained in joint fluid by systemic administration despite the equivocal observations of Linner,[10] Robinson,[14] and Anderson.[2]

The findings of Herrell[8,9] and of Dawson[6] are of considerable importance for though the local instillation of penicillin into a joint lends itself readily to the treatment of a purulent arthritis of one of the larger joints, it is less applicable where one or more small joints are affected. The present study was undertaken to define more clearly the extent to which penicillin administered intramuscularly penetrates into joint fluid.

Seven patients with hydrarthrosis affecting one or more joints were studied: 5 of the patients had typical rheumatoid arthritis and 2 an atypical disease which was probably rheumatoid arthritis. In Case 4 alone was the joint studied severely inflamed. Cases 1, 2, 5 and 6 received 25,000 units of penicillin in 2.5 ml. of normal saline intramuscularly every 3 hours. Cases 3, 4 and 7 received 40,000 units.

In each instance samples of serum and joint fluid were obtained simultaneously ½, 1, 2 and 3 hours after the subject had received the 8th dose of penicillin. In 4 instances, Cases 2, 3, 5 and 6, samples were obtained 3 hours after the 16th dose and in Case 3 additional material was obtained 3 hours after the 24th dose.

Methods. The concentrations of penicillin in both the blood sera and the joint fluids were determined by the cup assay method as modified by Cholden.[3] The diameter of each cup was 9 mm. *Staphylococcus aureus* which was sensitive to 0.016 units of penicillin per ml. was used as the test organism. It was grown in nutrient broth for 18 hours and then 0.1 ml. was inoculated into 20 ml. of melted nutrient agar and plates were poured. The undiluted synovial fluids and blood sera were delivered in 0.1 ml. amounts into the cups, and after incubation at 37° C. for 18 to 24 hours the areas of inhibition of growth were measured. As suggested by Foster and Woodruff[7] a standard penicillin curve was determined with each day's experiment, and the amount of penicillin present in the sera and joint fluids interpolated from this curve.

Results (See Table 1). In all cases penicillin was found to penetrate readily into the joint fluids resulting in essentially equal amounts of penicillin in the joint fluid and blood serum 1 hour after its administration. As previous investigators have shown[11] the serum concentrations fell rapidly after 1 hour and at the end of 3 hours little or no penicillin was detectable in the serum. However, our results show that in the joint fluids the concentration of penicillin decreases more slowly, and that there are appreciable amounts of penicillin present in the joint fluid 3 hours after its administration. This slow loss of penicillin from joint fluid is in agreement with the work of Rammelkamp and Keefer[11] who detected penicillin in joint fluid 13 hours after penicillin was injected directly into the joint. Though penicillin disappears

from the joint fluid more slowly than from blood serum, it does not accumulate. This is shown in Table 1 by the concentrations found in the joint fluid after the 2nd day of penicillin administration and in 1 instance after the 3rd day.

TABLE 1.—PENICILLIN IN BLOOD SERUM AND JOINT FLUID

Case No.	Wt. (lb.)	Dose I.M. (units)	Joint	W.B.C. joint (fluid)	Penicillin (units/ml.)	1st day ½ hr.	1 hr.	2 hr.	3 hr.	2nd day 3 hr.	3rd day 3 hr.
1	150	25,000	Knee	10,000	Blood serum	0.24	0.20	0.05	0.0		
					Joint fluid	0.24	0.15	0.10	0.05		
2	155	25,000	Knee	2,500	Blood serum	0.20	0.10	0.0	0.0		
					Joint fluid	0.20	0.20	0.05	0.0	0.07	
3	170	40,000	Knee	5,000	Blood serum	0.27	0.20	0.12	0.05		
					Joint fluid	0.24	0.24	0.20	0.14	0.14	0.14
4	177	40,000	Ankle	6,500	Blood serum	..	0.40	0.10	0.0		
					Joint fluid	..	0.30	0.15	0.05		
5	134	25,000	Knee	2,300	Blood serum	0.30	0.27	0.17	0.05		
					Joint fluid	0.20	0.22	0.22	0.17	0.15	
6	110	25,000	Knee	10,000	Blood serum	0.30	0.20	0.12	0.05		
					Joint fluid	0.17	0.20	0.20	0.15	0.15	
7	214	40,000	Knee	5,000	Blood serum	0.22	0.19	0.12	0.05		
					Joint fluid	0.17	0.19	0.15	0.13		

Rammelkamp and Keefer[13] have shown that a marked antibacterial effect against *Staphylococcus aureus* is obtained in whole blood and serum with concentrations of 0.039 and 0.156 Florey units of penicillin per ml. Hemolytic streptococci, pneumococci, meningococci and gonococci are generally considered more sensitive to penicillin than *S. aureus*.[4,6,8] The joint fluid of the cases studied 1 hour after administration of penicillin showed amounts of penicillin varying from 0.15 to 0.24 units per ml., levels well within the antibacterial level for staphylococci. The 3 hour determinations of 6 of the 7 joint fluids contained 0.05 to 0.17 units per ml., amounts still in the lower range of antibacterial activity for staphylococci. Thus our findings indicate that amounts of penicillin which are antibacterial for the common pathogens invading joints are obtained in the synovial fluid by the intramuscular administration of penicillin in the doses discussed.

Summary. 1. Penicillin was administered intramuscularly to 7 cases of hydrarthrosis. Concomitant blood serum and joint fluid penicillin assays were determined at ½, 1, 2 and 3 hour intervals.

2. Penicillin when administered intramuscularly in 25,000 and 40,000 unit doses at 3 hour intervals was found to penetrate rapidly into joint fluid and attain levels comparable with those attained in blood serum.

3. Maximum antibacterial quantities of penicillin were found to persist longer in the joint fluid than in the blood serum.

4. Penicillin did not tend to accumulate in joint fluid.

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TYPHOID BACILLURIA AND UROLITHIASIS

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THE conditions under which an individual becomes a carrier of typhoid bacilli present considerable interest from a clinical as well as from an epidemiologic point of view. Excretion of typhoid bacilli in the stools is usually caused by specific infection of the bile passages where the bacillus thrives as in a culture medium. This process is particularly apt to occur in patients whose bile passages are in a state of functional or anatomic impairment following previous disease.

Transient bacilluria is a common event in typhoid fever and, when carefully looked for, is detected in between 20 to 50% of cases (Schottmueller,[6] Young[7]). Persistent urine carriers, however, are said to be considerably rarer than stool carriers, their percentage amounting to a few tenths of 1% up to 3% of convalescents, according to different statistics. In the case of these urinary carriers the determining factors of persistent bacilluria are a matter of conjecture.

It is not within the scope of this communication to review the urologic complications described in typhoid fever. Observations about pathologic conditions of the urinary tract connected with typhoid bacilluria are particularly scarce. Young,[7] Harries[1] and asso-

ciates mention occasional suppuration of the kidneys due to *B. typhosus*. Even cystopyelitis is usually regarded as an uncommon complication. We were able to find only one reference to the simultaneous occurrence of nephrolithiasis and typhoid bacilluria: C. Hirsch[3] quotes Krause, who saw among 24,500 typhoid convalescents during several years 0.2 to 3.3% urine carriers and simply mentions 5 cases of nephrolithiasis among them.

According to the experience of urologic practice dealing with urinary infections and urolithiasis the finding of typhoid bacilli in the urine together with a stone seems to be very rare. The statistics of H. L. Harrington,[2] for instance, do not mention a single case of typhoid infection among 480 cases of urolithiasis.

Within $1\frac{1}{2}$ years, 4 cases of urolithiasis together with typhoid bacilluria have been observed in the Medical Dept. A. and the Pediatric Dept. B. of our hospital. Their case histories are presented with the view of contributing material to the solution of the carrier problem.

The procedure for isolation of typhoid bacilli from the urine and their identification as performed in the Bacteriological Laboratory of our hospital (Chief, Dr. Gurewitz) is as follows: The urine is centrifuged and a loopful of the sediment streaked out on a McConkey plate. To the remaining sediment 5 cc. of ox bile and nutrient broth in equal parts are added. In positive cases a pure culture (grayish, transparent colonies) of gram-negative bacilli is obtained after 24 hours. A few colonies of this growth are transferred separately into tubes containing double-sugar (Russell's) medium. On this medium typhoid bacilli show the following behavior: no gas is formed but slight acidity in the butt of the tube is produced. The sugar row used afterwards for identification is as follows: acid and no gas from dextrose, maltose and mannitol, no acid on lactose; indol not formed. Then an agglutination test is carried out using an anti-serum of a titer of 1:2000.

Blood is taken for culture into bile broth and after incubation of 24 hours a loopful is streaked out on a McConkey plate and the procedure described above is followed.

According to this procedure the typhoid nature of the bacilli in all of our cases was established.

Case Histories. Case 1. A. J., 19 years old, was admitted to the Surgical Dept. B of this hospital in December 1941. He had a stone in the right ureter and another one in the left kidney. He suffered from pain and showed hematuria. His blood pressure was 150/85. A ureterotomy was performed and the stone removed (Dr. Kook). Urine culture revealed *Staphylococcus aureus* and *B. proteus* before and after operation. The stone contained urates, phosphates and oxalates. His recovery was delayed briefly by mild and short postoperative bronchopneumonia. In February 1942, he returned to us because of pain in the left lumbar region. He emphasized even on close questioning that he had felt well all the time except for the pain he mentioned, and that he had had no fever since leaving the hospital. Urine analysis showed 1 to 2 erythrocytes and 80 to 100 leukocytes per high power field. *B. typhosus* was cultured from the urine. A second operation was performed and a stone was removed from the left kidney (Dr. Kook). Typhoid bacilli were cultured from within this stone. The temperature rose to 40° one day after operation;

high fever lasted for 11 days accompanied by relative bradycardia until the temperature finally dropped by lysis. His consciousness was slightly impaired, his tongue was heavily coated. He had the appearance of a patient sick with typhoid. The Widal reaction was positive 1 day after operation, but the organism was not cultured from the blood or stool, whereas urine cultures were always positive during his stay in the hospital. Pyuria persisted, *B. proteus* and *B. pyocyaneus* also being found in the urine. A dose of 24.5 gm. of sulfapyridine was of no avail. He remained under observation of the medical clinic and although he felt well all the time, urine cultures remained positive. Mandelic acid was administered following the suggestion of Kleeberg[4,5] who successfully used this material in a number of typhoid cases; two courses failed, however, to rid him from the infection. In June 1943, pain in the left lumbar region reappeared and reached the intensity of colics accompanied by fever. On admission to the Medical Dept., the Widal agglutination test showed a titer of 1:1000 for *B. typhosus* and 1:200 for *B. gaertner*. The urine contained many red and a few white cells and although a Roentgen picture failed to reveal a stone, its presence was clinically almost certain. The urine showed again a heavy growth of *B. typhosus*, this finding being positive also in specimens taken separately from both ureters. After cystoscopy his temperature rose to 40° for 4 days accompanied again by bradycardia and leukopenia. He received 25 gm. of sulfapyridine, which finally cleared the infection, a result which since then has been verified several times.

CASE 2. A. Ch., 36 years old, was admitted to the Medical Dept. A, in June 1942, on the 11th day of his disease. He was ill with typhoid fever of a fairly severe form but not very toxic in character. Blood cultures were positive several times. Fever did not drop for several months. Because of this unusually prolonged fever a thorough clinical, laboratory and Roentgen ray examinations were performed. Besides a mild and short bronchopneumonia no focus of infection was revealed. It must be stressed that the findings of urine examinations and cultures were negative. On August 21, for the first time, many leukocytes and a few erythrocytes were found in the urine and this finding persisted for about 1 month after which period examinations became negative. On October 18, an intravenous pyelography was performed and a small stone in the middle third of the left ureter as well as dilatation of the urinary passages above the stone were detected. On October 19, *B. typhosus* was cultured from a urine specimen for the first time, on the 26th the patient had a typical left side renal colic. The patient who had been carefully questioned several times only then recalled that about 1 year earlier he had had a similar attack. He was not able to remember on which side—but remembered to have been advised by his physician to have a Roentgen ray taken, a stone being suspected. He had disregarded this advice and neglected the matter. Simultaneously with the attack mentioned above, his temperature now rose to 40°. On October 25, the stone was removed from the left ureter (Dr. Ehrlick). The urine remained infected by typhoid bacilli for more than at least 1 month, until he finally left the hospital. Both mandelic acid and sulfapyridine administered in several series failed to influence the typhoid fever and mandelic acid did not succeed to clear his urine after the operation. To sum up, in this case of typhoid a stone in the ureter apparently existed before specific bacilluria started.

CASE 3. L. K. K., a boy, 8 years old, was admitted to Pediatric Dept. B on April 21, 1941, in a severe general condition, following a febrile disease of 10 days duration. The diagnosis was typhoid fever complicated by otitis media. The urine was normal. No particular treatment was administered and on the 30th day of his disease the temperature dropped to normal. Ten days later, the boy was sent home, no cultures of the urine having been made.

About ½ year later the patient was brought to the out-patient clinic, showing signs of balanitis and paraphimosis. The reason for this balanitis was seen in a paraurethritis and for further investigation the boy was transferred to the skin clinic. Since the local condition was not improved and no reason for its

persistence could be detected, the patient was again admitted to the Pediatric Service. This time many leukocytes were found in the urine, in the first as well as in the second portion, and *B. typhosus* was cultured from the urine. In pus from the paraurethra, streptococci were found. An attempt to influence the balanitis by sulfonamide medication was unsuccessful. When searching for the reason of pyuria and typhoid bacilluria, Roentgen ray examination revealed an "ausguss" stone in the left kidney pelvis and dilated calices. During his stay in the hospital subfebrile temperatures were frequent and urine cultures always showed growth of *B. typhosus*. A severe pyodermia and eczema of the head and face made surgical intervention inadvisable at least for a certain time, and only after his skin infection had cleared up, a nephrolithotomy was performed (Dr. E. Joseph). The patient ran a febrile course for the first 10 postoperative days. During the early postoperative period typhoid bacilli disappeared from the urine but after a few days urine cultures became positive again. Mandelic acid, in a 6 gm. daily dose given for 12 days, did not clear the infection. The boy finally left the hospital in a good condition, but still showing pyuria excreting typhoid bacilli.

In this case *B. typhosus* was found 6 months after the final stage of typhoid fever. The urologic examination performed because of pyuria and bacilluria revealed nephrolithiasis.

Case 4. Y. N., a boy, $11\frac{1}{2}$ years of age, was admitted to the Pediatric Dept. B. on Dec. 18, 1942, because of high fever which was diagnosed as typhoid. The urine was normal. He received treatment by autohemoinjections following a method introduced by Dr. E. Rabinovitz. On the 13th day of the disease his temperature dropped to normal. Ten days later the temperature rose again, this time showing an irregular course of a character not usually observed in recurrences of typhoid. His temperature finally became subfebrile. The only abnormal findings in this period were pyuria and urine cultures positive for *B. typhosus*. Stool cultures were negative. On Roentgen ray examination of the urinary tract a large "ausguss" stone was found in the right kidney pelvis and a smaller one in the right ureter. During cystoscopy urine specimens were separately taken from both ureters for bacteriologic examination. Only the specimen taken from the right, *i. e.*, stone carrying side, showed *B. typhosus*. The boy's blood pressure was 125/80 at that time, a blood pressure definitely too high for this age. It was decided to remove the stone from the ureter first and this operation was performed (Dr. E. Joseph). When recovering from this operation, the boy fell ill with a severe and stubborn pyodermia. His blood pressure, incidentally, rose to 135/90. When the boy recovered at last from the skin complication the removal of the stone from the kidney was decided upon. But, on opening the lumbar region a big paranephritic abscess was cut open and the operative procedure was brought to an end by draining this abscess; when the wound cavity finally closed, the child had to be sent for convalescence because of his bad general condition. In this case urolithiasis and typhoid bacilluria persisted a few days after the fever had dropped. To our regret and in spite of our efforts we did not succeed in getting in touch with these 2 boys for follow-up examination.

A definite relation between bacilluria in general and pathologic conditions of the urinary tract exists. Heavy and prolonged excretion of bacilli in the urine may produce at least two urologic disease conditions—acute or chronic inflammation and development of stones. the resulting cystopyelitis is in itself a contributary factor for the formation of stones. On the other hand, stones similar to other disturbances of the urinary flow tend to maintain infections otherwise probably transient in character.

In the 2 adult cases lithiasis most probably existed before the

typhoid infection. It seems evident that a causal relationship exists between prolonged bacilluria and lithiasis. The particular conditions which are produced by stones in the urinary tract (urostasis, cystopyelitis) tend to prolong a temporary excretion of bacilli, in itself so frequent in typhoid, to a continuous bacilluria, a mechanism which is generally recognized as operative in urinary infections. As for the 2 children the circumstances are less clear. With both of them, lithiasis was diagnosed after their having recovered from typhoid. In both cases the stones showed the typical shape of an "ausguss" stone, as commonly found complicating urinary infections. It is also known that such a stone sometimes needs only a short time for its formation. We have seen cases, in septicemia, where a stone of this type developed within 2 weeks. Moreover, when we take into consideration the comparative rarity of urinary calculi in children it seems probable that those stones were formed in consequence of an acute infection by typhoid bacilli. We are, of course, not able to deny definitely their existence prior to the typhoid fever since urologic and anamnestic data are lacking for the period anteceding typhoid.

We believe that urinary calculi may condition a prolonged typhoid bacilluria, or, if formed as the result of the bacilluria, may maintain it persistently. We consequently think it advisable to perform a Roentgen ray examination of the urinary tract in urinary excretion of typhoid bacilli.

Summary. It is pointed out that, whereas the conditions under which a patient becomes a permanent excretor of typhoid bacilli from the bowels are known to a certain extent, information about urologic lesions conditioning typhoid bacilluria is limited.

Four cases are reported in which typhoid bacilluria coincided with urolithiasis: in 2 adult cases urolithiasis existed before the excretion of typhoid bacilli; in 2 children, stone formation seemed to follow typhoid bacilluria.

In the light of experience with other infections of the urinary tract the relationship between typhoid bacilluria and urolithiasis is discussed and its possible clinical and epidemiologic importance is emphasized.

Conclusion. From the foregoing it is evident that the relationship between urolithiasis and typhoid bacilluria is of clinical and epidemiologic importance.

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HUMAN INFECTION WITH BACTERIUM NECROPHORUM

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The last decade has seen the general use of anaerobic techniques in clinical bacteriology. This has contributed to the isolation and recognition of organisms which do not grow under the ordinary aerobic bacteriologic techniques formerly held to be adequate for clinical purposes. Media containing the sulfhydryl compounds (thioglycollic acid or its salts, cysteine and so forth) are used today to obtain anaerobic conditions. It has been our policy for some years to inoculate all material sent to the laboratory for bacteriologic studies into media containing thioglycollic acid, as well as the usual standard aerobic media. As a result, we were able to isolate and identify *B. necrophorum* from 3 human cases, an organism which usually is found only in domesticated animals.

Buhler, Seely and Dixon[1] have reviewed the literature of *B. necrophorum* in man. One case presented by Cunningham[2] had pulmonary involvement, but the organism was identified after postmortem examination. Shaw and Bigger[5] reported the isolation of *B. necrophorum* from the sputum of a male Negro with a lung abscess, who made an uneventful recovery after surgical intervention.

Dack and his co-workers[3] have reported the largest series of cases of infection with *B. necrophorum* in man. Their criteria of identification was similar to that of Orcutt[4] who studied the organisms obtained from infected domesticated animals.

Case Reports. Case 1. M. J. L., white, 37 year old male, admitted with history of chills, fever, and a productive cough present for 6 days prior to admission. Past history was entirely negative and there was no contact with animals. He complained of a sharp pain on the right chest wall extending back to the right scapula. Physical examination showed a well-developed, alert subject with a foul breath. Moist crackling râles were heard at the right base. The temperature was 38.8° C. Roentgen ray findings suggested a possible lung abscess. Laboratory examinations were negative except for a leukocytosis (16,400 per c.mm., 84% neutrophils) and a foul smelling sputum having a butyric acid-like odor. The aerobic culture revealed little of significance. Anaerobically, a pleomorphic, long-branched and occasionally filamentous organism was isolated. It failed to grow aerobically and on 2 occasions the organism was lost on transplants. It fermented glucose, maltose and levulose. Gelatin was not liquefied. Indole was obtained from tryptophane broth. A green zone appeared at the end of 10 hours around each colony when exposed to air after anaerobic incubation for 3 days on blood agar plates. The organism failed to reduce nitrates and did not produce H_2S. A number of transplants were required to obtain the organism in pure culture because

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of an accompanying gamma streptococcus. Regimen of sulfadiazine was instituted. Twenty-four gm. over a 4 day period was without effect on sputum production or odor. The patient was quite uncomfortable and complained of "chest" pains. Iodides and arsenicals over a period of next 11 days were ineffective. The patient's temperature remained "spikey." The Roentgen ray examination after the 13th hospital day showed no improvement. Daily sputum amounted to approximately 400 cc. A thoracotomy was performed on the 19th day after admission and the patient began to improve rapidly. He was discharged on the 11th week after surgery. The sera agglutination as well as complement fixation were positive for *B. necrophorum* 7 weeks after discharge from the hospital. A suspension of the organisms in 1 cc. saline introduced subcutaneously into 2 rabbits produced the typical necrotic lesions characteristic of *B. necrophorum* infection.

CASE 2. A 22 year old white girl with arrested pulmonary tuberculosis complained of a gradually increasing tenderness in the right axilla for 4 days. No history of exposure to animals was given. She was afebrile on admission but developed an elevated temperature (38° C.) on the 2nd hospital day. A fluctuating, tender, walnut-sized mass was felt on palpation. After 3 days on sulfadiazine and hot magnesium sulfate soaks, the abscess was incised. About 20 cc. of ill-smelling pus welled out. The abscess was evacuated, flushed with 5% sodium sulfadiazine. The wound drained for 6 days and then slowly closed without further ado. She was discharged on the 17th day after hospitalization.

Direct smear from the pus showed a small gram-negative, branched organism. It was a strict anaerobe and proved to be *B. necrophorum*. The complement fixation test was positive for this organism. Unfortunately no agglutination tests were carried out on the serum. However, typical lesions in rabbits were produced when the organisms were injected subcutaneously.

CASE 3. A 32 year old white soldier complained of "sore throats" and "stuffing of the nose and ears" for 6 months. Palliative treatment was of no avail and a month later he reappeared with history of pain in the left upper jaw. A dark left maxillary sinus was observed on transillumination. The patient was afebrile. Routine laboratory examination of blood and urine was normal. Antral irrigation washed out a foul smelling pus. Bacteriologic investigation proved the organism to be *B. necrophorum*. The soldier had not been exposed to animals. Activated zinc peroxide and iodides were without effect. Penicillin, locally and parenterally were used. A Caldwell-Luc operation was performed about 6 weeks after admission. Patient made an uneventful recovery. Due to technical difficulties we were unable to do serologic examination for the organism. Rabbit inoculations of the cultured organism produced characteristic lesions described by Orcutt.[4]

Summary and Conclusion. 1. The importance of routine anaerobic as well as aerobic bacteriologic techniques has been stressed.

2. Three cases of infection with *B. necrophorum* are presented. All recovered. No history of exposure to domestic animals was obtained.

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UNILATERAL DIAPHRAGMATIC FLUTTER

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Disturbances of diaphragmatic motility fall into several categories. One group, characterized by clonic contractions of the diaphragm, includes singultus and is the most common of all. Another group, less common than the first, is produced by tonic contractions of the diaphragm and occurs in tetany, tetanus, and hysteria. Under these conditions dyspnea as well as pain near the attachment of the diaphragm to the ribs may be found. A third group in which abnormal, irregular contractions of the diaphragm are seen is occasionally observed in tics and chorea.

In a particularly rare form the whole diaphragm or parts of it contract at a rapid rate causing the appearance of special symptoms and signs which enable the clinician to make the diagnosis often without resort to laboratory facilities. We had the opportunity to observe an example which presented unusual features.

Case Report. S. P., 84 year old male, was admitted November 11, 1944, complaining of headache, vertigo, and occasional chest pain. Rarely ill, he began to experience dizzy spells in 1943; no loss of consciousness occurred at any time. Almost simultaneously the patient began to suffer from headaches. In 1944 the patient had a slight attack of "influenza." Six weeks before admission to the hospital spells of vomiting occurred. For the past 5 years he had complained of cough and had expectorated white mucus which was occasionally blood-tinged. He was accustomed to sleep on 3 pillows at home and also reported some exertional dyspnea. He was confined to bed for a few months prior to admission because he felt too weak to walk. The patient was a heavy smoker. Until 11 years before admission he had worked in a paint factory mixing lead pigments.

On admission the temperature was 37° C., pulse rate 70, and respiratory rate 20. The emaciated, slightly dehydrated patient lay quietly in bed in no acute distress. He was oriented as to time and place, but responded slowly to questions. Examination of head, eyes, ears, nose, and throat was essentially negative. The chest was markedly emphysematous with flaring of the lower ribs. Breathing was mainly abdominal. No thrills or pulsations were felt or seen in the anterior or posterior chest wall. Percussion and auscultation of the lungs revealed the typical findings of an advanced emphysema. Percussion of the heart was rendered uninformative by the emphysema. The heart sounds were distant and rhythmic. No murmurs were heard. The blood pressure was 140/80 mm. Hg. At the base of the heart the cardiac sounds were so faint as to be almost inaudible.

In the lower right chest peculiar rapid sounds varying in intensity from time to time were heard. These sounds usually were louder, clearer, shorter, and higher pitched than the heart sounds. The fast rate and the absence of any accentuation made these sounds resemble fetal heart sounds (embryocardia). Despite the high rate it was always possible to count them because each examiner instinctively counted in the same manner as he would count the heart beat, 2 beats constituting 1 cycle. In this way it was found during an observation period lasting 16 weeks that the rate varied between 250 and

300 beats per minute with the average rate being 270 beats per minute. The point of maximum intensity of these sounds was located in the fifth and sixth right interspaces just lateral to the mid-clavicular line. These sounds were also heard posteriorly from the inferior angle of the right scapula to the base of the lung. Slightly louder on expiration, they seemed superficial as if they were coming from just below the chest surface. The sounds were not heard in the left chest at all. They were present during all phases of respiration as well as when the patient stopped breathing.

Inspection of the abdominal wall showed, on one occasion only, slight rapid fluttering movements in the right upper quadrant just below the border of the ribs. Over the abdomen the flutter sounds were not audible and all physical findings were negative.

Neurological examination was essentially normal.

Laboratory data were not remarkable; only a few of the findings will be recorded. Red blood cells, 4 million; hemoglobin, 13 gm. per 100 cc.; leucocyte and differential counts were normal. The urine revealed 1+ albumin, with few red blood cells, epithelial cells, and no casts. Blood sugar was 78 mg. per 100 cc.; urea nitrogen 12.5 mg. per 100 cc. Blood Wassermann and Kahn tests were negative. Sedimentation rate (Westergren) was 11 mm. in 15 minutes and 22 mm. in an hour. Blood calcium was 10.7 mg. per 100 cc. Venous pressure was 65 mm. All other findings were also in the range of normal values.

Following the discovery of the abnormal sounds the patient was further questioned and he related that he had been aware of "something going up and down like a clock all the time" in the right chest at the level of the right diaphragm. He had experienced this sensation for the first time about a month before admission to the hospital. He added that there was some pain in this area; since the distress was worse at night, it interfered with his sleep. After a few weeks in the hospital this pain disappeared as did the clock-like sensation. The abnormal sounds, however, were audible as ever to the examiners.

The abnormal sounds were heard regularly up to November 28 when they became less constant and were occasionally missed. When absent, the sounds could always be restored by having the patient cough or breathe deeply.

Figure 1 shows that the rate of the abnormal sounds bore no apparent relationship to the heart rate or to the respiratory rate. Coughing made the sounds louder and faster. On the several occasions that the patient was examined during sleep the abnormal sounds were never heard.

The electrocardiogram showed a regular sinus rhythm without evidence of myocardial damage. Using silver electrodes and needles placed subcutaneously in different locations around the area where the sounds were most audible, we tried to register some abnormal activity of the diaphragm, but all attempts failed.

Roentgenograms revealed a prominent aortic knob with evidence of calcification of the aorta. The heart was normal in size and shape. The lungs showed evidence of emphysema and increased markings. An old healed fracture of the left tenth rib posteriorly was found. Several kymographic, roentgenographic, and fluoroscopic examinations of the diaphragm with the patient standing as well as in the lateral position were carefully made, but these failed to show any abnormal movements. Skull plates were negative.

Twice the right phrenic nerve was blocked successfully by novocaine. During the first attempt the abnormal sounds persisted for 15 minutes after fluoroscopy indicated paralysis of the right diaphragm. Then they disappeared only to return immediately by having the patient cough. In the second attempt the abnormal sounds persisted during the entire period that the right diaphragm was paralyzed. This time, however, small rapid flutter movements were visualized under the fluoroscope in the lateral half of the otherwise stationary right diaphragm.

Electroencephalograms showed normal brain patterns.

The recording of the abnormal sounds (Fig. 2*A*) taken from the sixth right interspace in the right axillary line revealed rapid regular beats with a rate of

272 per minute. The heart sounds were registered immediately thereafter but the pulmonary emphysema made the registration difficult. Figure 2*B* shows the stethogram of the heart sounds obtained from the fifth left intercostal space and left mid-clavicular line where the cardiac sounds were heard best.

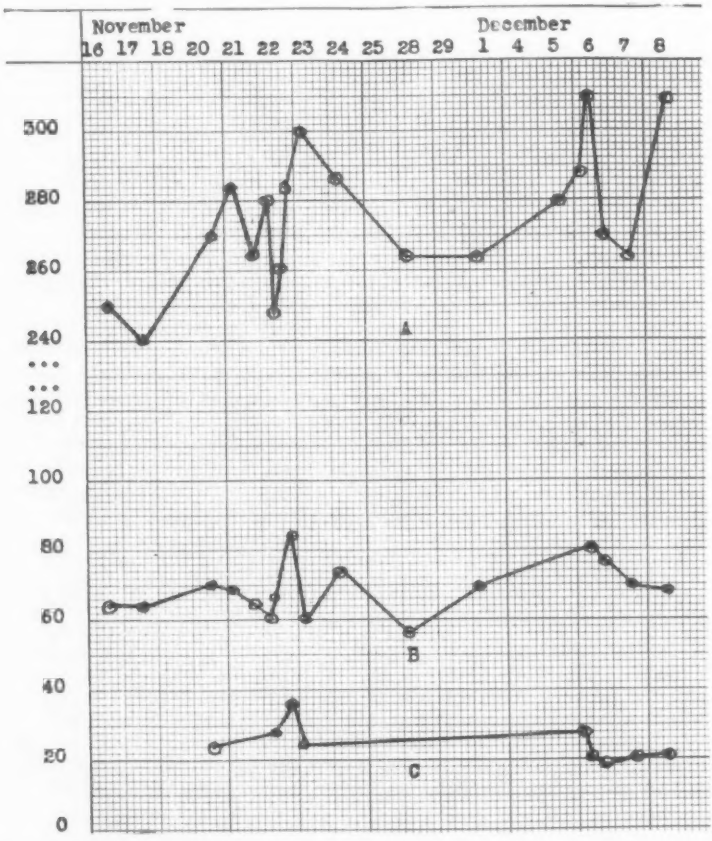

FIG. 1.—No relation is visible between the rate of the heart (*B*) or the respiration (*C*) and the rate of the abnormal sounds in the chest (*A*).

Quinidine sulfate, 3 grains every 2 hours for 26 doses, was given. Under this régime the abnormal chest sounds disappeared, but could be elicited again by coughing or deep breathing. Whereas previously these sounds, if produced by these maneuvers, would last for a considerable time, they now remained only for a few seconds. This effect disappeared a few days after quinidine was discontinued. The patient was dismissed after an observation period of 16 weeks, during which the abnormal phenomenon was observed. Occasionally it disappeared; however, it would again reappear for short periods.

Discussion. The finding of rhythmic sounds, resembling fetal heart sounds and bearing no relationship to cardiac activity, in the right chest of an 84 year old male is unusual enough to demand recording. Review of the literature on disturbances of diaphragmatic activity

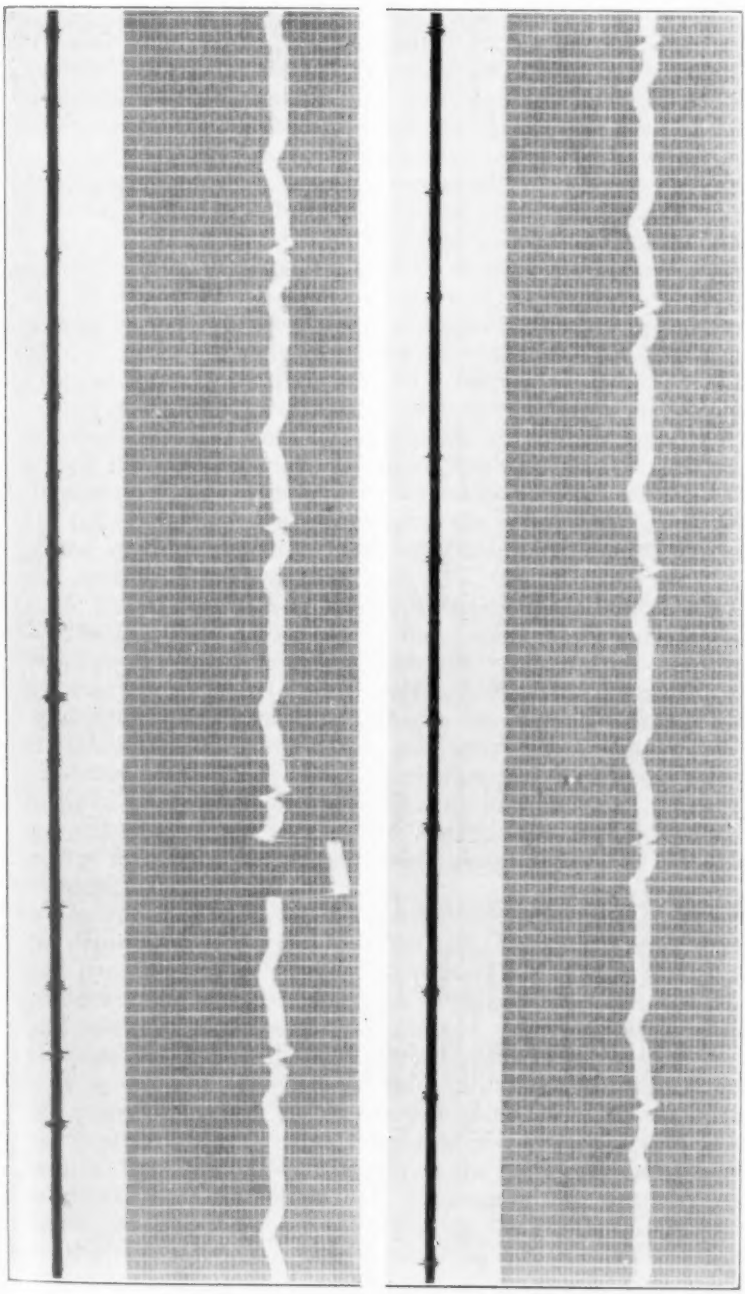

FIG. 2.—*A*, The stethogram of the abnormal sounds and the electrocardiogram in Lead II. *B*, The heart sounds registered from the apical area with the electrocardiogram in Lead II.

TABLE 1.—REPORTED CASES OF DIAPHRAGMATIC FLUTTER (TIC)

Author	Year	Sex	Age	Clinical picture	Diagnosis	Rate/min.	Fluoroscopy	Etiology	Treatment	Result	Miscellaneous
Gamble *et al.*[4]	1925	M	38	Dyspnea, pain in left arm; small, rapid bilat. thor. excursions; pres. asleep	Postencephalitic tic of diaphr.	84	Abnor. bilat. spasmodic contr. of d.	Encephalitis	Ethyl chloride spray	Temp. relief	
Dowman[3]	1927	F	67	Sharp precord. pain, later epigas. pain; rapid, pure abd. resp.; "fluttering of heart;" intermittent attacks lasting 1 hr. and longer	Postencephalitic diaphragmatic tic	90–130	Bilat. flutter of d.	Encephalitis	Freezing and section of phrenic	Cured	
Skillern[10]	1931	F	37	Harassing attacks of rapid resp. lasting a few min.; spasm of facial muscles; rapid, shallow, bilat. chest movements	Postencephalitic diaphragmatic tic	200	Bilat. flutter of d.	Encephalitis	Bilateral phrenicectomy	Cured	Entire relief not obtained until complete ablation of thor. segment of r. phrenic through chest done
Smith[11]	1932	F	20	Jerky breathing with hiccoughs; marked resp. grunts; absent during sleep	Diaphragmatic tic	100–140	Right d. more involved; rapid flutter	Following appendectomy	Sect. of r. later l. phrenics	Phenomenon temp. disappeared	
Smith[11]	1932	F	21	Rapid, jerking, grunting, spasmodic resp.; absent during sleep	Diaphragmatic tic	120	Tic of r. and l. d.	Encephalitis	Sect. of r. phrenic	Impr'd for 3 mos.	
Porter[9]	1936	M	57	Anginal-like pain; jerky resp.; reg. abnor. bilat. chest sounds	Diaphragmatic flutter	250+	Bilat. flutter of d.	(See Misc.)	Phrenic block with novocaine	Temp. relief	Later reported by 2 other writers as a poss. hysteria in psychopathic inf. male; they tried bilat. phrenicotomy with only temporary relief[5,12]
Handron[6]	1941	F	36	Sev. up abd. pain related to meals; bilat. vibration of up. half of body; pain l. shoulder; occ. vom.; splashing sounds in abd.; resp. grunts; attacks intermittent	Diaphragmatic tic	128	Bilat. clonic contr. of d.	Fol. pyloric stenosis operation	Resection of both phrenics	App. cured	Patient had repeated intestinal obstructions

reveals only 1 case that is at all similar. First described in 1936 by Porter, this same case has been reported several times as the patient traveled from one hospital to another giving different histories each time.[5,9,12] That patient, 57 years old when first described in 1936, complained of angina-like pain. Abnormal sounds independent of cardiac activity could be heard over the entire lower third of the chest anteriorly and posteriorly with a rate of 250 to 300 beats per minute. Registration of these sounds was possible. Fluoroscopy revealed bilateral symmetrical flutter movements of the diaphragm.

The individual reported in this article is definitely not the same one described in previous papers. In this case the sounds were caused by the rapid contractions of one part of the right diaphragm which showed normal respiratory movements. No case of this type seems to have been reported. It is interesting to note that the rate and character of the abnormal sounds were similar in both cases. In our patient these sounds were heard only over a circumscribed area and fluoroscopy revealed normal respiratory movements of the diaphragm. Only following block of the right phrenic nerve with paralysis of the right diaphragm could fluttering movements be seen in one small area of the right diaphragm corresponding to the point of maximum intensity of the abnormal sounds. Blocking of the phrenic nerve in this case did not stop the phenomenon.

In Table 1 are listed 7 cases, including the observation reported by Porter, in which the rate of the diaphragmatic contractions was rapid (over 80 per minute) and the clinical data were complete. No attempt is made here to list cases of diaphragmatic disturbances which do not fulfil the above two requirements. In none of these cases with the exception of Porter's were abnormal chest sounds caused by abnormal contractions of the diaphragm heard. These disturbances followed encephalitis or appeared after an abdominal operation. It is worth while to note that in these cases block or section of the phrenic nerves repeatedly led to immediate disappearance of the abnormal diaphragmatic contractions.

The appearance of painful sensations with abnormal contractions of the diaphragm, as was found also in our case, is known, easily explained, and does not require further comment.

Most of the reported cases have followed some form of encephalitis and produced such respiratory distress that surgical operation on the phrenic nerves with varying success had to be done.

It seems that there are several mechanisms through which this condition may occur. (1) In cases in which this phenomenon results —encephalitis and perhaps from hysteria, abnormal central stimuli coming down the phrenic nerve from the brain may cause rapid contractions of the diaphragm. (2) Abnormally fast contractions of the diaphragm may be observed displaying the rhythm and rate of the heart of the individual. This is not at all rare in experiments on dogs in which the left half of the diaphragm occasionally contracts rhythmically with the heart. One of us often saw these unusual contractions in the dog disappear immediately if the left phrenic nerve were removed

from the heart or severed caudad from the heart before it reached the diaphragm. The potentials due to cardiac activity produce enough stimuli to cause contractions of the diaphragm. Under normal conditions these stimuli are not strong enough, but apparently suffice if the sensitivity of the diaphragm is altered during an experiment by anesthesia, exposure, or drugs. (3) It also seems certain that pathologic changes as found in diaphragmatic pleurisy (particularly following pulmonary infarctions) or in peritonitis also lead to abnormal contractions of the diaphragm. Pathologic changes in the diaphragmatic muscle are very common in these various conditions.[7]

In the case reported here, the assumption seems justified that we are dealing with a purely peripheral disturbance. Successful blocking of the phrenic nerve did not abolish the phenomenon and there was no relationship to cardiac activity. In an attempt to explain the mechanism of the abnormal phenomenon, the comparison with attacks of paroxysmal tachycardia of the heart is obvious. From animal experiments it is known that stimulation of heart muscle whose metabolic state has been altered through some sort of damage (as anemia) may lead under certain circumstances to a long series of rapid abnormal contractions (paroxysmal tachycardia, flutter, or fibrillation).[1,2] This happens particularly if the stimulus is applied in a certain early phase of diastole called the "vulnerable phase."[13] It is possible that a similar mechanism existed in a small part of our patient's diaphragm. In favor of this explanation is the fact that once the phenomenon disappeared, it could always be brought back by cough or deep respiration, that is, by renewed stimulation of the injured diaphragmatic muscle. It was always present when the patient breathed deeply and was absent when the patient was asleep, that is, during more superficial breathing. Accordingly we may be dealing with an abnormal response of a small part of the diaphragm to physiological stimuli. Porter's case with the symmetrical fluttering of both halves of the diaphragm cannot be explained in this way.

With regard to the viewpoint expressed by Lewis and Dock[8] that the contraction of the heart muscle does not contribute to the origin of the first heart sound, the appearance of loud sounds caused by contraction of a part of the diaphragm in our case is of particular interest. These sounds need, however, not be attributed to muscular contractions alone. Vibrations due to stretching of connective tissue in tendinous parts of the diaphragm may be responsible.

Conclusion. A case of unilateral diaphragmatic flutter in an 84-year-old man is reported, and recorded, in which rapid loud rhythmic sounds in the right chest independent of the heart sounds led to the clinical diagnosis. These sounds were caused by contractions of a part of the right diaphragm.

ADDENDUM: The patient was reëxamined on June 13, 1945, and October 4, 1945. He stated that he had occasional recurrence of the clock-like sensations in the right chest. No abnormal sounds were heard during normal respiration or after coughing on both occasions.

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INTESTINAL LIPODYSTROPHY (LIPOPHAGIA GRANULOMATOSIS OR WHIPPLE'S DISEASE)

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and

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Patients who present as their major complaint, diarrhea, either chronic or of short term duration, usually receive intensive study in order to establish an etiologic (or anatomic) diagnosis. However, many cases of chronic diarrhea are diagnosed incorrectly or signed out with a diagnosis wanting. We wish to report a case of intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease) as it is the 14th such case to be reported and with the hope that another cause for chronic diarrhea might be further established.

Since Whipple's[12] first description of intestinal lipodystrophy there have been 12 cases reported in the literature. This disease occurs predominantly in males usually between the 4th and 6th decade. Among the major complaints are diarrhea with or without blood, sometimes steatorrhea, postprandial discomfort and distention, asthenia and weight loss. They usually further present a moderate anemia, normal leukocyte and differential counts, hypotension, skin pigmentation and achlorhydria. Necropsy findings are consistent. These show a mesenteric lymphadenopathy with lipoid replacement

of these lymph nodes, and enlarged intestinal villi with characteristic fat-laden cells in the mucosa and submucosa.

In no case, including our own, was the diagnosis of intestinal lipodystrophy made antemortem. The most frequently entertained antemortem diagnosis have been, regional ileitis, ulcerative colitis, sprue, Boeck's sarcoid and Hodgkin's disease. Table 1 presents all the cases reported to date in a form which we have slightly modified from the paper of Apperly and Copley.[1] It is worth mentioning that in 3 cases, Whipple,[12] Apperly and Copley[1] and our own, an exploratory laparotomy was performed during the course of the illness and Hodgkin's disease or sarcoma, Hodgkin's disease, and questionable tuberculosis, were respectively reported from mesenteric lymph node microscopy.

TABLE 1

	Whipple	Blumgart	Blumgart	Blumgart	Fleischman	Jarcho	Boeck	Korsch	Hill	Rheinhart	Sailer	Copley and Apperly	Vaux	Amsterdam and Grayzel
Sex	M	M	F	M	M	M	M	M	M	M	M	M	M	M
Age	36	42	44	32	38	37	45	60	60	74	45	51	49	54
History, time in yrs.	5	2	2	1½	1	15	1	10	¼	1	5	4	9?	2
Post. prand. discom. and disten.	0	+	0	0		+	+		?	+	+	+	+	+
Asthenia and weight loss	+	+	+	+	+		+	+	+	+	+	+	+	+
Diarrhea	+	+	0	+		+	+		+	0	0	+		+
Diarrhea with blood		0	+	0		+					+	+	+	+
Steatorrhea	+	+	0	0		?	+			0			+	0
Fever		0	0	0		?			0	0			0	+
History of arthritis	+	0	0	0	+	+					+	+	+	0
Skin pigmentation	+	0	0	0		+				0	+			+
Skin pigmentation, icterus slt.		+	0	0		0				0	+	+	0	0
Edema, moderate		+	+	0		0				+	+	+		+
Anemia, moderate	+	+	+	+		+	+	+	+	+	+	+	+	+
Leukocytosis	0	0	0	0		0	0	0	0	0	0	0		0
Eosinophilia	+	0	0	0								+		0
Low blood pressure		+	0	+					+		+	+	+	+
Achlorhydria		+		+		+	+				+	+	0	
Terminal acidosis	+	?				?	?		?	?	0	?	?	0
Terminal tetany			+	+									?	0
Autopsy Findings														
Pericarditis, fibrous	+	*	+	0	+	+		+	+	*	+	0	+	0
Endocarditis	+	*	0	0		+		+		*		0	0	0
Pleuritis	+	*	0	0		+			+	*	+	0	0	0
Peritonitis	+		+							+		+	0	+
Hemorrhages	+		0	0	+	+						0	0	0
Enl. intest. villi with fat cells	+	+	+	+	0	+	?	+	+	+	+	+	+	+
Mesenteric lymphadenopathy	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chylous ascites	0	0	+	0						+	+	0	0	0
Pancreatic fibrosis, moderate	0	0	0	0	+		0	0	+	+	+	0	0	0

+ and 0 indicate presence or absence of symptom or sign.
Blank space—symptom not recorded.
* Examination of thorax not permitted.

Case Report. L. K. (278817), a Jewish white man, age 54, was admitted to the Jewish Hospital of Brooklyn on October 26, 1944, complaining of diarrhea, abdominal distention and loss of weight.

In 1942 the patient was admitted to another hospital complaining of diarrhea of 3 weeks' duration. Following an intensive study an exploratory laparotomy was performed and revealed "firm whitish adhesions of the lower small intestines, with a few whitish areas, and numerous soft nodes along the aorta and spine." Microscopic examination of the areas and nodes were reported as "(1) chronic peritonitis of the ileum, (2) chronic lymphadenitis, probably tuberculous, (3) possibly healed regional ileitis." He was readmitted several times to the same hospital with exacerbations of his symptoms. In August, 1943 progressive pigmentation was noted on both lower extremities. Roentgen ray studies of the gastro-intestinal tract were interpreted as showing a deficiency pattern. In April, 1943 he was admitted to another hospital where

a gastro-intestinal study was made which proved negative. He was maintained on a high vitamin, low fat diet.

Five days prior to his admission to this hospital diarrhea began again, unassociated with pain. Daily postprandial distention was noted for about 3 hours, and a fever of 100° to 101° F. was recorded for the 6 weeks prior to admission. His stools were described as brown, liquid, not foamy or foul-smelling, and no melena was noted. He felt weak and listless. There was no history of arthritis.

On admission the patient was a pale, thin, emaciated white man with a dry scaly skin and a markedly distended abdomen. The blood pressure on several occasions ranged from 82 to 110 systolic and from 40 to 68 diastolic. The lungs were clear to auscultation and percussion and an apical systolic murmur was heard. The abdominal wall was slightly edematous. Peristalsis was visible and auscultation revealed normal peristaltic sounds. Rectal examination was negative. Peripheral edema was slight.

Almost throughout his hospital stay his temperature ranged between 100° and 102° F. Several Roentgen ray studies of the gastro-intestinal tract were interpreted as representing a deficiency pattern. Guinea pig inoculation of the stool failed as the animal died prematurely of secondary infection. The radiology department ventured a Roentgen ray diagnosis of regional ileitis principally involving the terminal ileum, as the ileal coils appeared narrowed and had serrated borders. Roentgen ray examinations of both hands were negative. Urine analysis on several occasions revealed specific gravities ranging from 1.002 to 1.010 with traces of albumin but no sugar. Blood counts showed hemoglobins ranging from 48 to 67% with red blood counts ranging from 2.19 to 3.28 million per c.mm. A typical blood count read: hemoglobin 50%, R.B.C. 2.88, W.B.C. 6,450, polymorphonuclears 72, bands 8, lymphocytes 15, monocytes 5, eosinophils 0. The sedimentation rates were 27 and 40 mm. per hr. and the stools consistently showed 1 to 4+ blood, with no ova or parasites found. The total blood protein ranged from 3.17 to 5.3 mg. % with from 2.9 to 3.1 mg. % globulin, and 1.0 to 1.3 mg. % albumin with an A/G ratio of from 2.2 to 3.1 The blood urea nitrogen, CO_2 combining power, uric acid, calcium and cholesterol values were within normal limits. Blood agglutination for the typhoid-Salmonella group was negative. A tuberculin test was negative in 1:100,000 dilution.

Despite a great deal of parenteral therapy including whole blood transfusions, amino acids, glucose and vitamins, he continued to go downhill. His diarrhea continued and abdominal distention was always present. Toward the end he had several bouts of melena and died on December 19, 1944 on his 55th hospital day.

Necropsy. The body was that of an emaciated white man weighing 40 kg. The peritoneal surfaces were dull and the mesentery was thickened and studded with easily palpable, firm lymph nodes. The heart weighed 220 gm. and was grossly not unusual. The lungs showed no evidence of tuberculosis; the right and left lungs weighed 300 and 340 gm. respectively. Their cut surfaces were not unusual. The tracheobronchial lymph nodes were likewise not unusual. The jejunum presented a thickening of the valvulæ conniventes. The mucosa was purple-red in color, and between the thickened valvulæ the mucosa had a velvety appearance. The proximal ileum presented a similar picture, but the terminal ileum was thickened. The serosa of the terminal ileum was covered with occasional white, flat, plaques measuring up to 1.4 x 0.9 cm. These areas were firmer than the surrounding tissue. The mucosa of the terminal ileum presented ulcerations underlying the white plaques described. The mesentery was markedly thickened and studded with lymph nodes measuring up to 1.2 x 1 x 1 cm. They were firm, grey-white in color and not matted together. On section, they were gray-white but no cystlike spaces were seen. The liver weighed 1210 gm., and its external surface was red brown in color. On section the cut surface showed a nutmeg appearance. The pancreas weighed 52 gm. and was yellow-tan, and on section showed the normal lobular pattern. The suprarenal glands together weighed 17 gm. and

were grossly not unusual. The right and left kidneys weighed 155 and 185 gm. respectively. The capsules stripped with ease and the external surfaces were red-brown and glistening. On section the cut surfaces bulged; the cortex was easily demarcated from the medulla. The spleen, musculo-skeletal system, and bone marrow were not unusual.

Microscopic. Aside from the gastro-intestinal tract and mesenteric lymph nodes there was nothing of note. The pancreas showed no fibrosis.

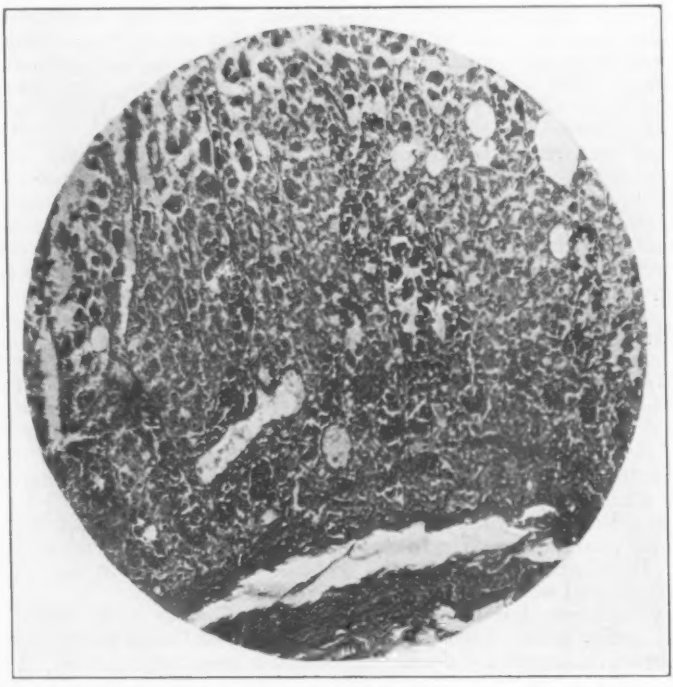

FIG. 1.—Photomicrograph of jejunum showing foam cells in the lamina propria. H. and E. × 100.

In preparations from the jejunum (Fig. 1) the villi were prominent and blunted. In many places the entire mucosa was ragged and necrotic. Crypts found in the mucosa were few in number and were greatly distorted. Large, foamy, mononucleated cells were seen in the mucosa, some of these cells lying within thin-walled endothelial-lined spaces. In some areas these foamy macrophages comprised the most prominent cell seen. In no place were giant cells seen. The remainder of jejunal coats were not unusual. In preparations from the terminal ileum the villi were decidedly blunted and the mucosa here also showed a marked necrosis. However, there were no large foamy cells seen in the mucosa. In preparations from the ileocecal region the mucosal pattern approached a more normal architecture.

In preparations from the mesenteric lymph nodes, under low power the cytoarchitecture was markedly distorted. (Fig. 2.) The glands were composed of numerous thin-walled endothelial-lined spaces presenting an almost swiss-cheese pattern. Even under the low magnification large foamy macrophages could be seen. Under a higher magnification (Fig. 3) these spaces could be seen to be filled with large foamy macrophages with vesicular nuclei. The remainder of the lymph node consisted of nests of foam cells and islands

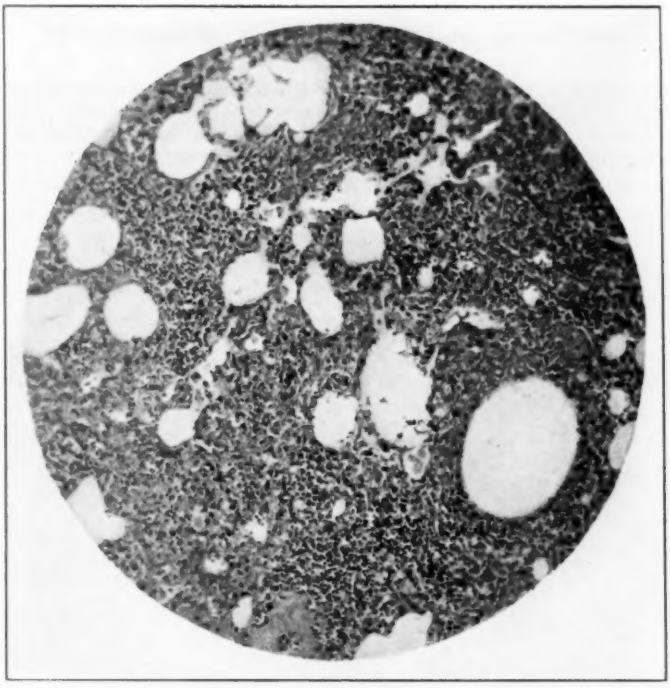

FIG. 2.—Photomicrograph of lymph node showing cystic spaces and foam cells. H. and E. × 100

FIG. 3.—Photomicrograph of lymph node showing the foam cells under higher magnification. H. and E. × 400.

of lymphoid tissue, and also occasional multinucleated giant cells. In preparations stained with Scharlach R (Fig. 4) these foam cells were seen to contain orange granules. These cytologic characteristics were seen in all of the mesenteric lymph nodes studied.

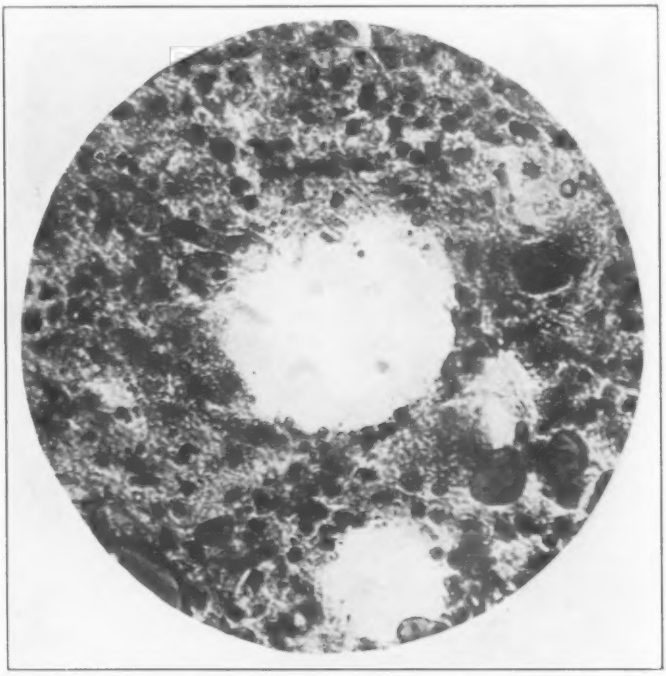

FIG. 4.—Photomicrograph of lymph node showing the large cells filled with fat. Scharlach R. × 400.

Discussion. The cause and the pathologic physiology involved in intestinal lipodystrophy remains obscure. There are, however, several theories on record to explain the clinical and pathologic findings. Ryle[9] states that chronic fatty diarrhea on a pancreatic basis is overstressed, while disease involving the absorbing mechanism has not received sufficient attention. Blockage of the lacteals with subsequent fatty diarrhea has been reported by a number of investigators.[6,7,9] In no case of intestinal lipodystrophy has obstruction to the thoracic duct or cysterna chyli been found, although such obstruction does lead to chylous ascites and lymph node changes as seen in this disease. Jarcho[7] suggests the possibility of some congenital malformation in the mesenteric lymph nodes as the cause for this disease.

The dilatation of the mesenteric lymph node spaces is the most consistently found lesion in this disease. Hill[5] believes that there is dilatation by chyle with subsequent breakdown of the emulsion and inspissation. Clinically, intestinal lipodystrophy is very similar to the sprue syndrome but the latter does not, or only rarely, presents intestinal changes as seen in Whipple's disease. Fairly and Mackie[4]

report 3 lymphoblastomas which gave rise to a sprue syndrome and believed that malabsorption of food products was the cause for the diarrhea. Blumgart[3] also regards malabsorption as the primary factor. Along similar lines Reinhart[8] believes that there may be an increased excretion of fat into the intestines. And finally the liberation of lipolytic ferments from damaged cells results in fat and fatty acid stasis in lymph nodes. The saponified fats are engulfed by giant cells and eventually there is further chronic inflammation, fibrosis and obstruction.[1,10]

The fever presented by our case could be explained on the constant presence of decubitus ulcers, and occasional phlebitis resulting from almost continuous intravenous therapy.

The diagnosis of intestinal lipodystrophy presents obvious difficulties. However, when more cases are reported, a pattern of symptoms and signs may make it easier. Within the past 8 years, 9 of the 14 cases have been reported; the most recent, by Vaux.[11] The treatment of this disease must remain symptomatic until an etiologic basis is discovered. Parenteral therapy with vitamins, glucose, protein hydrolysates and transfusions offer the most for these patients. Boeck[2] used pancreatin with no success.

Summary. 1. A case of intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease) is presented.

2. The literature is reviewed and the theories for its mechanism and pathologic physiology are presented.

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STEVENS–JOHNSON SYNDROME

(Eruptive Fever With Stomatitis and Conjunctivitis)*

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Two cases of an interesting and uncommon syndrome of an eruptive febrile disease associated with stomatitis and conjunctivitis, originally

* I wish to thank Major B. Neilson, Chief of the Dental Service, Major H. Simons and 1st Lt. B. Capus, of the Eye, Ear, Nose and Throat Service, for their valuable aid in administering local therapy.

described by Stevens and Johnson,[7] are reported here. These cases were encountered within a 2½ week interval with no history of possible contact with each other.

This syndrome has been referred to, at times, as "erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth,"[1] or "erythema exudativum multiforme with ophthalmia and stomatitis."[3] However, because of the characteristic clinical picture, it may well be that we are dealing with a distinct clinical entity. Pending further knowledge concerning the etiologic agent, the term "Stevens-Johnson syndrome" or "eruptive fever with stomatitis and ophthalmia"[4] may be applied. Certainly this syndrome differs from erythema exudativum multiforme which is manifested by a cutaneous eruption, mild constitutional symptoms and only mild, if any, oral and ocular involvement. Murphy[6] has noted that the enanthem rather than the exanthem appears to be the most constant feature of the disease. It has been suggested[4] that the syndrome may be a severe or atypical form of erythema exudativum multiforme (Hebra) and that the name "Hebra" be replaced by "Stevens-Johnson."

The clinical course is characterized by the acute onset of fever and prostration, associated with a cutaneous eruption, a severe membranous stomatitis and a purulent conjunctivitis. The oral lining is usually edematous and covered with numerous vesicles which soon rupture. This is followed by the formation of a thick membranous exudate which then sloughs off. The purulent conjunctivitis is usually severe. Panophthalmitis and either partial or total blindness are frequent complications. A macular-papular or vesicular eruption, which varies in severity in individual cases, may be present. The course usually lasts about 2 to 3 weeks and may be followed by a recurrence.[3] A leukopenia or mild leukocytosis is present. There are no characteristic laboratory findings. No light has been thrown on the etiologic agent. Bacteriologic studies have not been illuminating. Staphylococci or streptococci have been isolated from the lesions[1,4] but these may have been secondary invaders. A case associated with Vincent's infection of the mouth has been reported.[2] No transmissible agent was recovered by Edgar and Syverton[3] following animal inoculation of the vesicular fluid from one of their cases. Biopsy of a skin lesion failed to yield any significant findings.[3]

Case Reports. CASE 1. T. K., a 19 year old white male student, was admitted February 6, 1944 from the dispensary of the City College of New York because of a sore mouth of 1 day duration. The soldier had been well until 1 week prior to admission when he began to have a sore throat, for which he took some cough medicine containing "coccillana bark, tolu and menthol." He denied having taken any other drugs. On the day prior to admission his mouth became painful and he noticed "blisters" on his lips and on the lining of his mouth. These symptoms increased in severity, and on reporting to his unit medical officer on the following day he was sent to the station hospital.

The past history was not significant. He had measles, mumps and chickenpox in childhood. Venereal diseases were denied.

There was no history of familial diseases.

Physical Examination. The soldier was alert, coöperative, oriented and not acutely ill. The temperature was 101.2° F. The skin was clear. The

mucosa of the mouth was somewhat edematous, and numerous vesicles, 0.1 to 0.3 cm. in diameter, containing clear fluid, were present over the entire oral lining including the buccal mucosa, tongue, palate and lips. The conjunctivæ were mildly injected. The lungs were clear. The heart sounds were of good quality and no murmurs were heard. The pulse and ventricular rates were 100. The blood pressure was 120/82. The abdomen was soft and the liver and spleen were not palpable. The extremities were not remarkable. No abnormal neurologic signs were present and there was no lymphadenopathy.

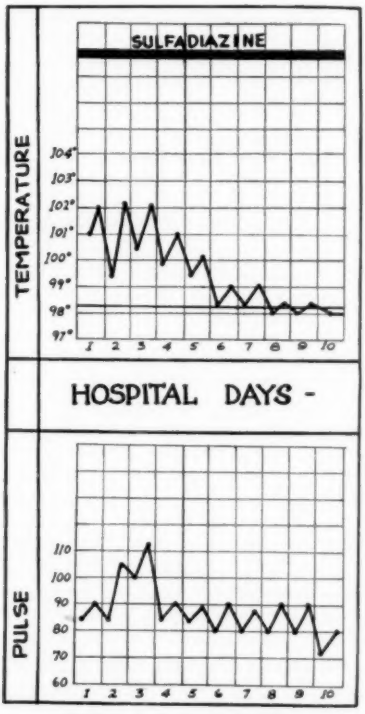

FIG. 1.—Course of Case 1.

Course. During the first 2 days following admission the patient became progressively more acutely ill and toxic. The vesicles of the mouth ruptured spontaneously, and a thick grayish membranous exudate formed over the entire lining of the mouth and pharynx. This membrane peeled off easily, leaving angry red areas. The conjunctival injection increased in severity and he began to have a profuse yellowish purulent discharge from both eyes.

On the 3rd day his condition began to improve and he appeared less toxic. At this time the membranous exudate of the mouth began to slough off in plaques of 0.2 to 0.4 cm. in thickness, leaving superficial red areas of ulceration. The patient began to complain of a mild dysuria and, upon examination of the penis, erythema and superficial crusting were noted at the urethral orifice.

The dysuria and external urethritis cleared up completely within 2 days and the purulent ocular discharge began to diminish. Progressive improvement in the general and local conditions continued. By the 10th day the oral membrane had sloughed off and by the 17th day the mucous lining was completely restored. The ocular discharge ceased entirely by the 7th hospital

day. The conjunctival injection, however, subsided more slowly, persisting until the 17th day.

The temperature remained elevated for the first 3 days after admission, ranging between 102° and 102.5° F. It then subsided by lysis and reached a normal level on the 6th hospital day, after which the patient remained completely afebrile.

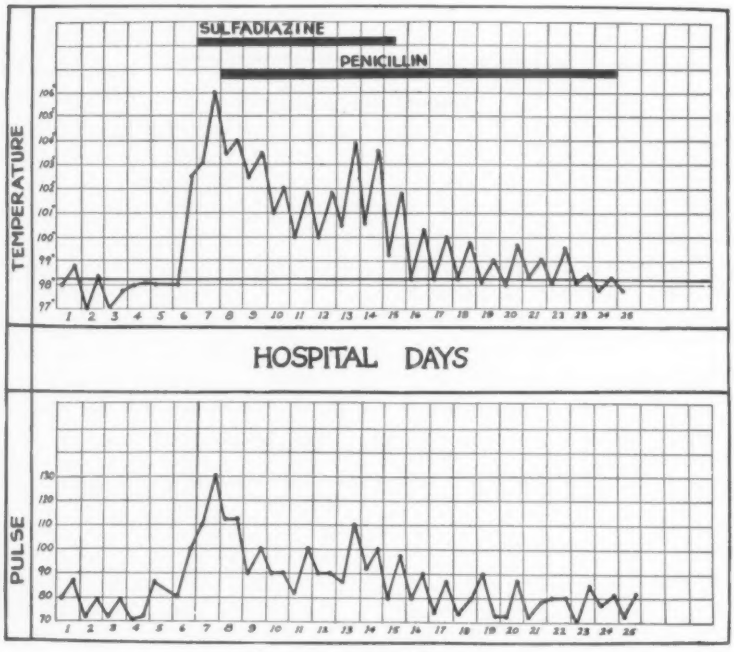

FIG. 2.—Course of Case 2.

Sulfadiazine therapy was started on the 2nd day and continued for 12 days. Six grams were administered daily for the first 4 days and 4 gm. daily for the last 8 days. The mouth was treated with peroxide mouth washes, 2% gentian violet applications and saline mouth irrigations. Under supervision of the Eye, Ear, Nose and Throat Service the eyes were treated with saline irrigations and 5% sodium sulfadiazine eye drops during the acute phase, and thereafter with 0.25% zinc sulphate solution. Vitamins were administered in the form of A and D capsules, thiamine chloride and ascorbic acid.

The patient was discharged on the 26th day in excellent general health. He was completely asymptomatic and no oral or ocular residua were present, with the exception of a somewhat smooth appearing tongue.

Laboratory Data (CASE 1). Blood Counts:

Hospital day	W.B.C.	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Hb. (%)
2nd	14,200	55	29	11	5	..	90
4th	8,550	51	28	18	2	1	
6th	9,550						
8th	9,550						
10th	7,300						

Urine examinations and blood cultures were repeatedly negative. Hemolytic streptococcus was the predominating organism on culture of the throat.

The nose and throat culture for Klebs-Loeffler bacilli was negative. A smear of the mouth failed to reveal Vincent's organisms. No fungi were noted upon examination of the oral membrane. The smear of the ocular discharge showed many polymorphonuclear leukocytes but no organisms, and a culture revealed staphylococcus albus. Roentgen ray of the chest was negative. The blood Kahn was negative. Blood agglutinations for typhoid, paratyphoid, tularemia and undulant fever were negative. The Weil-Felix reaction and heterophile antibody test were negative. Determinations, at frequent intervals, of blood sulfadiazine concentration resulted in values which ranged between 5.7 and 8.3 mg. per 100 gm. of free drug.

CASE 2. M. N., a 19 year old white male soldier, was admitted from the infirmary of New York University to the station hospital on February 22, 1944. He had been well until 3 days prior to admission when he began to feel feverish and developed pain and slight swelling below the lobe of the left ear. One day prior to admission 3 gm. of sulfadiazine, in divided doses, were administered by the medical officer of the unit. On the day of admission when the swelling increased in degree, a diagnosis of mumps was made and he was sent to the hospital.

The *past history* was not contributory. He had measles, chickenpox and pneumonia in childhood. There was no history of allergy. About 1 year prior to admission the patient developed a "right submaxillary cellulitis." It was incised and drained, and a sulfonamide drug administered for about 1 week. He denied ever having contracted venereal disease.

The family history was irrelevant.

Physical Examination. The soldier was coöperative, alert and not acutely ill. The temperature was 98° F. The skin was warm and dry. A 2-inch well-healed surgical scar was present over the right submaxillary region. A moderate swelling, confined to the parotid gland, was noted below and anterior to the lobe of the left ear. The orifice of the left parotid duct was prominent and erythematous. The lungs were clear. The heart sounds were of good quality and no murmurs were audible. The pulse and ventricular rates were 80. The blood pressure was 126/84. The abdomen was soft and no masses were palpable. The liver and spleen were not felt. The extremities were not remarkable. There was no lymphadenopathy. The neurologic examination was negative. A diagnosis of mumps parotitis was made on admission.

COURSE. The patient remained afebrile during the first 5 days following admission. Swelling of the left parotid gland persisted. On the 6th day after admission his temperature rose to 102° F. The palpebral and bulbar conjunctivæ became markedly injected, and a moderate bilateral chemosis and mucopurulent ocular discharge developed. In the evening he began to experience some soreness of the mouth. On the following day the temperature rose to 106° F. and the patient appeared very acutely ill, extremely toxic and prostrated. The entire mucosal lining of the mouth was somewhat edematous. Numerous pearly vesicles were noted on the surface of the tongue. They contained clear fluid and varied in size from 0.2 to 0.5 cm. in diameter. Several irregular areas of thin grayish membranous exudate were present on the surface of the buccal mucosa and the lips. A few small scattered vesicles appeared on the skin; 3 on the palm of the left hand, 3 on the trunk, 4 on the face and 1 on the glans of the penis. They were surrounded by a thin zone of erythema and were 0.2 to 0.4 cm. in diameter. The external urethral orifice was erythematous. Upon specific inquiry the patient admitted having mild dysuria. It was felt at this time that the clinical picture resembled the Stevens-Johnson syndrome with characteristics of an eruptive fever, stomatitis and conjunctivitis. Oral sulfadiazine therapy was started with an initial dose of 4 gm. Thereafter 1 gm. was administered every 4 hours.

On the 8th hospital day he was still acutely ill, although the temperature had dropped to 104° F. The membranous exudate formation and the edema of the oral lining became more marked. The cutaneous vesicles increased in size and slightly in numbers, and a thin membranous exudate appeared at the urethral orifice. Because of the desperate condition of the patient, pen-

icillin therapy (40,000 units administered intramuscularly every 3 hours) was instituted and sulfadiazine was continued. At the suggestion of the dental service, the mouth was treated with topical applications of tyrothricin, containing gramicidin and tyrocidin.

FIG. 3 *A*

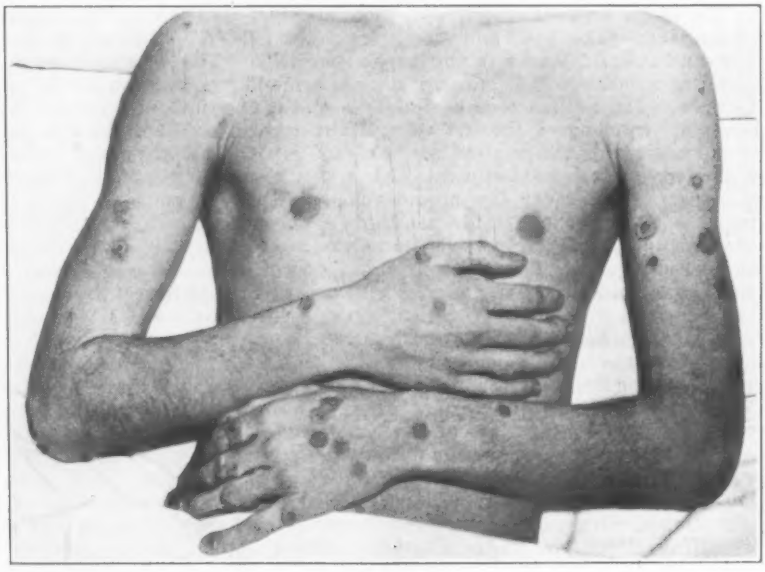

FIG. 3 *B*

On the 9th day the temperature ran to 103° F. and the patient appeared slightly improved, less toxic and somewhat more alert. The left parotid

swelling had subsided considerably but enlargement and tenderness of the right submaxillary gland became apparent. The ocular chemosis had diminished somewhat. The mouth was less edematous although the membranous exudate on its surface had become more extensive. The cutaneous vesicles increased somewhat in number and were particularly numerous on the hands and wrists. Elsewhere on the body they were few and sparsely distributed. The membranous exudate at the urethral meatus had increased in severity.

During the following 4 days his general condition slowly improved and the temperature gradually subsided to about 101.5° F. The swelling of the left parotid and right submaxillary glands disappeared and the ocular discharge diminished. The cutaneous vesicles of the trunk, face, arms, and forearms began to recede although those of the hands increased in size to form bullæ 0.5 to 2 cm. in diameter. The oral membranous exudate increased progressively. This soon covered the entire lining of the mouth, and thereafter grayish membranous plaques 0.1 to 0.2 cm. in thickness sloughed off slowly. The scrotum became completely covered with vesicles and this was followed by complete desquamation of the superficial epithelium, leaving a raw erythematous surface. Because of difficulty in swallowing and frequent vomiting, the fluid intake was maintained by continuous intravenous infusions.

FIG. 3 *C*

On the 13th day the temperature suddenly rose to 104° F. and the white blood count dropped to 5800, but no change in his general and local conditions were apparent. Because of the possibility of a sulfadiazine reaction, chemotherapy was discontinued. Penicillin therapy, however, was maintained.

The temperature slowly subsided until the 18th day when it reached normal limits and the patient remained afebrile thereafter. The soldier's general condition continued to improve and he began to take food by mouth. Penicillin therapy was decreased to 25,000 units intramuscularly every 3 hours on the 11th day, to 15,000 units every 3 hours on the 19th day and it was discontinued entirely on the 22nd day. A total of 2,700,000 units of penicillin were administered. Thiamine chloride and ascorbic acid were administered subcutaneously during the first 2 weeks. Thereafter they were administered orally, in addition to vitamins A and D, and nicotinic acid.

The skin lesions on the trunk, face, arms, and forearms had dried completely by the 18th day. However, the blebs of the hands increased in size by confluency to several centimeters. This process reached its height at about the 19th day, and thereafter these bullæ dried slowly. The fluid contents

remained clear, although several of these blebs became hemorrhagic on being subjected to trauma. By the 31st day the walls of all the bullæ had completely desquamated, leaving dry erythematous areas at their former sites. The superficial epithelium of the scrotum and glans was restored completely by the 29th day. The membranous exudate of the mouth continued to slough until the 36th day, leaving irregular areas of superficial ulceration which epithelialized rapidly. The lips, which showed considerable fissuring and superficial ulceration and bled with the slightest manipulation, gradually cleared.

FIG. 3 *D*

The ocular discharge, chemosis and conjunctival injection began to subside on the 10th day (4 days after onset of the conjunctivitis). On the 14th day adherent membrane on the palpebral conjunctiva bilaterally was noted by

the Eye Service. On the 41st day fine scarring of the conjunctival surfaces of the lids was observed. Two weeks later the Eye, Ear, Nose and Throat Service reported, "Fine scarring of the conjunctival surface of upper lids similar to Stage III trachoma. Symblepharon left lower lid." Mild to moderate bulbar and palpebral injection of the conjunctivæ persisted. No corneal involvement or vitreous opacities were noted at any time. The vision remained unimpaired. Local therapy included 2% aqueous sulfathiazole drops, 1% atropine, boric acid irrigations and compresses to the eyes in the acute stage. Thereafter penicillin ointment (5000 units/oz.), 0.125% neosynephrine solution, 0.8% sulfanilamide solution, and 1% silver nitrate solution were employed.

FIG. 3 *E*

FIG. 3.—Photographs taken 21 days after onset of initial symptoms of the Stevens-Johnson syndrome: *A*, Membranous exudate completely covered the tongue, and there was marked fissuring, excoriation and bleeding of lips. *B*, *C*, *D* and *E*, The bullæ of arms, forearms, lower extremities and trunk had receded considerably, and many showed central umbilication. Bullæ of the hands were still at their height. The superficial epithelium had desquamated from the scrotum and the glans penis.

Photographs were taken on the 26th hospital day (21 days after initial appearance of symptoms associated with Stevens-Johnson syndrome). By this time there had been considerable general and local improvement. Figure 3 shows clearly the cutaneous bullæ, many of which began to show central drying with umbilication. The stomatitis with membranous exudate completely covering the tongue is likewise clearly demonstrated.

Photographs were obtained again 1 week later (33rd day). Figure 4 demonstrates the further improvement which had occurred. Most of the cutaneous bullæ had dried completely. A few membranous plaques were still visible on the tongue.

The soldier was transferred on the 86th day to a general hospital for further local eye therapy. On transfer his general condition was excellent and he had gained about 15 pounds. Moderate bilateral chronic conjunctivitis and a small synechia between each lower lid and the contiguous scleral conjunctiva were present. However, there was no restriction in the movement of the eyeballs. Slight pigmentation at the sites of the previous cutaneous blebs was still present.

He was discharged from the general hospital after 2 weeks because of the progressive spontaneous improvement in the conjunctivitis.

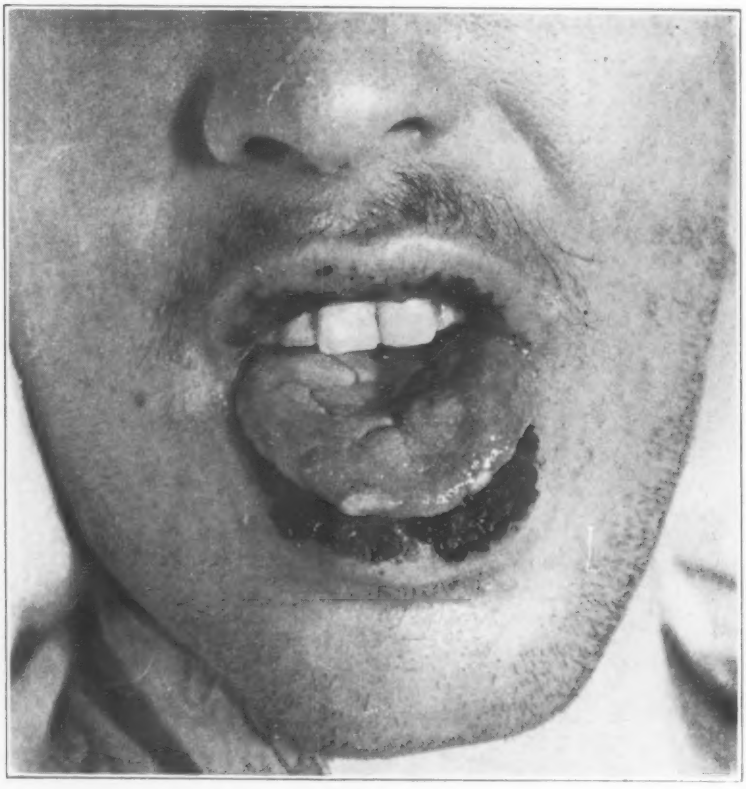

FIG. 4 *A*

Laboratory Data. Blood Counts:

Hospital day	W.B.C.	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Basophils (%)	Eosinophils (%)	Hb. (%)	R.B.C. (millions)
1st	5,300	38	49	9	1	3	90	.....
7th	10,950	74	26	..	..	..	95	4.920
8th	13,550	71	25	4	..	..	..	.....
9th	7,800	73	26	..	1	..	90	4.640
10th	8,250	67	29	3	..	1	..	.....
11th	5,800	61	39	..	..	..	..	.....
12th	9,100	..	..	..	..	..	..	.....
13th	5,100	68	31	..	..	1	..	.....
14th	9,600	34	62	..	1	3	..	.....
15th	..	..	..	..	..	..	96	5.340

A smear of the mouth failed to reveal Vincent's organisms. Examination of the oral membrane did not show the presence of fungi. Nose and throat cultures produced hemolytic streptococcus and hemolytic staphylococcus. The contents of the cutaneous vesicles repeatedly failed to reveal organisms on smear, and produced no growth on culture. No organisms were present

FIG. 4 *B*

FIG. 4.—Photographs taken 28 days after onset of symptoms of Stevens-Johnson syndrome. *A*, Grayish membranous plaques were still visible on the tongue. The lips were improved. *B*, the bullæ of the hands had dried. Reëpitheliazation of the glans had progressed.

on smear of the urethral meatus and a culture produced no growth. A culture of the ocular discharge yielded gram-positive diplococci. Blood cultures and urine examinations were negative. The blood N.P.N. was 30 and the blood sugar was 100. The blood Kahn was negative. Blood agglutination tests for typhoid, paratyphoid, tularemia and undulant fever were negative.

The Weil-Felix reaction and heterophile antibody tests were negative. Fifty-three intradermal skin tests for the common ingestants, contactants and inhalants were not contributory. Blood sulfadiazine concentrations ranged between 3.0 to 4.6 mg. per 100 gm. of the free drug.

Discussion. Case 1 presented the picture of severe membranous stomatitis, purulent conjunctivitis and involvement of the urethral meatus. No true exanthem was present, but this case clearly falls into this clinical syndrome. The acute course was short, lasting but 1 week, and the soldier made a complete recovery without complications. Oral sulfadiazine was administered in addition to local therapy to the mouth and eyes.

Case 2 was admitted to the hospital after Case 1 had completely recovered (17 days following admission of Case 1), and was kept under isolation for mumps. The 2 soldiers were students at different universities and at no time had they been in contact with each other. Six days after being admitted, Case 2 began to develop the typical characteristics of the Stevens-Johnson syndrome, *i. e.*, severe purulent conjunctivitis, vesicular and severe membranous stomatitis, associated with a vesicular and bullous cutaneous eruption. He became desperately ill and severely prostrated. Because of his precarious state both sulfadiazine and penicillin were administered. His course was extremely stormy throughout the 1st week and thereafter he improved slowly. The acute course lasted about 3 weeks. Although his vision remained unimpaired, a residual bilateral mild conjunctivitis and mild bilateral synechia remained. The effect of penicillin and sulfadiazine therapy cannot be evaluated in this single case. Certainly the response, if any, was neither dramatic nor prompt. Because of the history of having received a sulfonamide 1 year prior to admission and sulfadiazine 1 day before admission, a skin test to determine sulfonamide hypersensitivity was performed. The method described by Leftwich[5] was employed. Serum, obtained from a patient who had been receiving sulfadiazine for 5 days and which contained a free drug level of 7.7 mg. %, was used for the intradermal test. A negative result was obtained. Clinically the patient improved while receiving sulfadiazine therapeutically. Because of the negative intradermal test and improvement while under sulfadiazine therapy, the latter drug may be excluded from consideration as the causative agent.

Unfortunately these cases shed no further light upon the etiology of this bizarre syndrome. There was no evidence of sepsis or Vincent's infection in either case. The vesicles were sterile. Hemolytic streptococci, which were isolated from the throat cultures of both cases, may well have been secondary invaders. A strong impression exists that this syndrome is a systemic disease. It may well be that it is a virus infection with the clinical phenomena being toxic manifestations. Of interest is the fact that the symptoms in Case 2 were preceded by and associated with mumps (left parotid and right submaxillary). All doubt as to the diagnosis of mumps was dispelled when his roommate was admitted to the hospital, with mumps, 21 days following his admission date. In one previously reported case the symptoms

likewise started about 1 week subsequent to the onset of mumps.[3] It would be pure speculation at this point to hypothesize a relationship between this syndrome and mumps. However, a possibility arises that the virus of mumps in Case 2 was either the direct cause or indirectly predisposed the tissues to the entry of the etiologic virus. Further information must await investigation of future cases.

Summary. 1. Two cases of Stevens-Johnson syndrome of unknown etiology and characterized by an eruptive fever with membranous stomatitis, purulent conjunctivitis and severe constitutional reaction are reported.

2. These cases were encountered within a 2½ week interval with no history of contact with each other.

3. The first case was treated with sulfadiazine orally in addition to local therapy, and a complete recovery was made.

4. The second case was desperately ill and was treated with both sulfadiazine and penicillin. Following a protracted and extremely stormy course a complete recovery resulted, except for mild chronic residual conjunctivitis and bilateral ocular synechia.

5. The effect of either sulfonamide or penicillin therapy upon this syndrome cannot be properly evaluated from a review of these 2 cases.

6. A possible relationship of the etiologic agent to the virus of mumps is cited.

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EXPERIENCES WITH 2350 BLOOD TRANSFUSIONS AT AN ARMY GENERAL HOSPITAL IN INDIA

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During a 17-month period 2350 blood transfusions were given at this Army General Hospital in India, principally to combat troops. Approximately three-fourths of the transfusions were given to Chinese soldiers and one-fourth to Americans. Because of the lack of equipment commonly found in civilian blood banks, improvisation and modification of some techniques have been necessary. Experiences under these circumstances with transfusion reactions have emphasized

well established points concerning their cause and prevention. The use of universal donors for American patients has provided further evidence of interest in the current controversy regarding the advisability of this practice.

Development of the Transfusion Service. Among the first considerations when this hospital opened in April, 1943, was the establishment of a Blood Transfusion Service. Although an adequate supply of

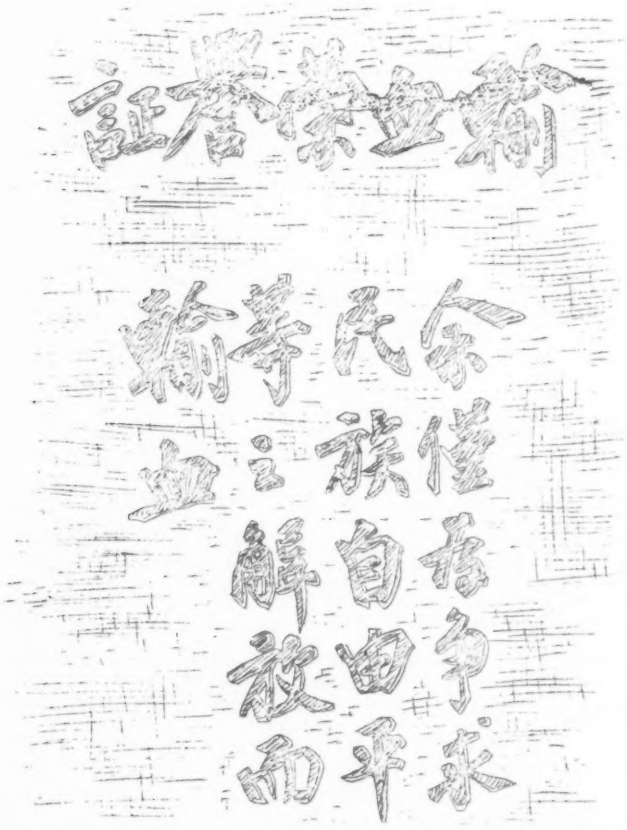

FIG. 1.—Certificate given to each Chinese blood donor. Translation: "I give my blood for liberty, equality, and the independence of China."

Red Cross plasma was available, the diseases endemic in this area and the tactical situation implied an early and steadily increasing need for whole blood. Typing sera were not available. They were obtained from medical officers and laboratory personnel of known types A and B and tested for potency. Blood transfusion apparatus was not available. Using commercial solution flasks with dental procaine carpules forced through holes in the rubber stoppers and tubing from plasma sets, a satisfactory semi-closed gravity system for

drawing blood was devised. Salvarsan burettes were used for administering blood. In May, 1943 the first transfusions were given and in June, 1943 the Chinese Blood Bank was opened.

An unusual and somewhat difficult problem has been the procurement of Chinese blood donors. The average, uneducated Chinese soldier, imbued since birth with the concept of personal thrift and unacquainted with the refinements of modern medicine, did not readily accept the idea of giving his blood to a fellow countryman unknown to him. As a result of much perseverance and tact on the part of our medical officers and the fullhearted coöperation of Lt. Col. An-Chuen Ma of the Chinese Army, this resistance is gradually being overcome. For many months a mobile blood procurement team visited Chinese units along the Ledo Road but at present Chinese donors are reporting to this hospital twice a week. Shown in Figure 1 is the certificate given to each Chinese blood donor.

For the first few months blood for American patients was obtained from members of the Medical Detachment by ward officers. In February, 1944 the increasing demand necessitated the establishment of a separate American Blood Bank, with donors reporting from many units in this area. Beginning with 17 transfusions during June, 1943 the number of transfusions each month steadily increased, reaching a maximum of 355 during July, 1944. From June, 1943 through October, 1944 the 17-month period covered by this report, a total of 2350 blood transfusions were given, 1732 to Chinese and 618 to American patients.

Methods and Techniques. Typing sera were obtained from suitable A and B donors and tested for potency by the method of Coca. Following inactivation they have been stored under sterile conditions.

For blood typing the open slide method of Vincent has been used. With typing sera of adequate strength it has proved to be very reliable. Not infrequently the blood type recorded on the donors' "dog tag" has been found to be incorrect. For compatibility tests the open slide method was used for several months. In February, 1944 this was abandoned in favor of the centrifuged test tube method of Levine because of its greater speed and more clear cut reactions. In the absence of macroscopic agglutination microscopic checks have been made routinely. Rh antiserum was not available for determining the presence or absence of the Rh agglutinogen.

Cold agglutinins have been sought for when indicated but no attempt has been made to identify other minor hemagglutinins or the sub-groups.

Only blood less than 7 days old with a negative Kahn and negative malaria smear has been used for transfusion. Despite the high incidence of malaria in this area, American donors with a negative malaria history have been available most of the time. In a few instances donors who had a single malaria attack more than 9 months previously have been used. No clinical or laboratory evidence of malaria transmission has resulted from these transfusions. In Chinese, because of the very high incidence of malaria and the difficulty in obtaining donors, the malaria history has been ignored, even though an attack occurred less than 1 month prior to the blood donation. Despite a negative blood smear, it is not unlikely that malaria was transmitted by some of these transfusions. Unfortunately the press of work prevented study of this problem. Malaria transmission would be difficult to establish with certainty in the Chinese because of the frequency of chronic recurrent malaria among the recipients and the possibility of a primary infection occurring while in the hospital.

In Americans the type O so-called "universal donor" was used for most of the transfusions. Intragroup transfusions were not feasible without an excessive waste of blood because of the unpredictability of the amount of blood and the blood types needed from day to day and week to week. Agglutinin titers of type O blood have not been determined because of the lack of sufficient laboratory personnel.

In Chinese patients intragroup transfusions were given almost exclusively. Because of the frequency of transfusions and the relatively rapid replacement of blood, the disproportion between the types of donors and recipients has not at any time been great.

The relative frequency of type B blood in the Chinese was striking. Table 1 shows the frequency in per cent of blood types of 1000 consecutive Chinese donors as compared with figures for the American white population taken rom a s tandard textbook.[9]

TABLE 1.—FREQUENCY (%) OF BLOOD TYPES OF CHINESE AND AMERICANS

International type	Chinese	Americans
O	39	44
A	28	40
B	26	10
AB	8	6

All donors have been tapped with the improvised semi-closed gravity apparatus mentioned above. Only 300 cc. of blood were taken from Chinese donors because of their smaller stature and correspondingly smaller blood volume. Sodium citrate (3.5%) prepared in our central dressing room was used as an anticoagulant, 50 cc. for 300 cc. of Chinese blood and 70 cc. for 500 cc. of American blood. Transfusions were given by the open method, pouring blood from the donor bottle through a gauze filter into a salvarsan burette. Commercial donor and recipient equipment (Baxter) has recently been received and it is planned to replace the present equipment with it.

Indications. The majority of the transfusions were given for shock and anemia due to blood loss in battle casualties. Large amounts of blood for individual patients have frequently been necessary, particularly in wounds of the cranial, thoracic, and abdominal cavities. During later months an increasing number of transfusions were given for sepsis, acute and chronic, with and without marked anemia. Less common indications were thermal burns, malaria with marked hemolysis, scrub typhus, and operative procedures associated with significant blood loss (*e. g.*, bone grafts).

Recently the effect of immuno-transfusion in scrub typhus was investigated on a small scale. Whole blood and pooled plasma from convalescent cases were given to patients in various stages of the disease, without apparent beneficial effect.

In this hospital there has been a marked preference for the use of whole blood over plasma in the treatment of battle casualties, both in the early stages immediately after wounding and during the later stages of definitive treatment. In contrast to the 2350 whole blood transfusions given during this 17-month period, there were only 934 transfusions of liquid and dried plasma. Although in some instances plasma has been given to deeply shocked patients while blood was being cross-matched, the use of plasma at any stage in the treatment of

battle casualties has been very infrequent. Most of the plasma transfusions have been given for severe thermal burns during the acute stage of plasma loss. In a few cases plasma has been used to correct hypoproteinemia not associated with significant anemia.

Chinese Plasma Bank. Because no source of plasma was available for the Chinese, a Chinese Plasma Bank was established in conjunction with the Chinese Blood Bank. Plasma from blood unsuitable for transfusion was pooled with suitable distribution of the blood types, creating a reserve of liquid plasma which has more than satisfied the requirements of this hospital. From June, 1943 through October, 1944 271 bottles (97,850 cc.) of this plasma have been used. At present there is a reserve on hand of 204 bottles (71,400 cc.), much of which will be sent to units in more forward areas. Pyrogenic reactions accompanying transfusion of this plasma have been frequent, averaging about 25%. There have been no hemolytic reactions.

Reactions to Blood Transfusions. Transfusion reactions have been divided into 3 groups: (1) hemolytic; (2) proteolytic, including allergic manifestations of all types and degrees of severity; and (3) pyrogenic, including chills and fever as well as fever alone. Of the 2350 transfusions, 482 have been complicated by reactions, an overall incidence of 20.51%. No reaction has been fatal. The number of reactions of each type and their relative percentages are shown in Table 2.

TABLE 2.—ANALYSIS OF REACTIONS IN 2350 BLOOD TRANSFUSIONS

Type of reaction	No.	%
Hemolytic	2	0.085
Proteolytic	79	3.361
Pyrogenic	401	17.064
Total	482	20.510

The two hemolytic reactions occurred during July, 1943. Both were in Chinese patients and were due to errors in typing. An incidence of 0.085% of hemolytic reactions compares favorably with figures reported in transfusion series of comparable size,[1,10] and with 0.18% in a series of over 40,000 transfusions collected by Kilduffe and DeBakey.[4] The laboratory technicians responsible for this record deserve much credit.

An incidence of 3.361% of proteolytic reactions is somewhat higher than has been reported in the United States.[3,4] It is thought that this may be due to a greater frequency of allergic manifestations in this area. A similar situation was found in skin disease. Although there have been a few instances of moderately severe angioneurotic edema, most of these reactions have consisted of mild urticaria. Anaphylactic shock has not occurred.

Because of the lack of adequate equipment and facilities for cleaning transfusion apparatus, pyrogenic reactions were relatively frequent for many months. Sodium dichromate and sulfuric acid were not available for cleaning glassware and there were no facilities for washing glassware or rubber tubing under pressure. Rubber tubing was of

necessity used far beyond the usual and desirable time for discard. The chief factor causing many of these reactions was the use of narrow-neck plasma bottles in Chinese donor sets. Removing pyrogens from these bottles, whose necks measure 6 mm. in diameter, was found to be extraordinarily difficult and uncertain without special equipment.

In August, 1944 adequate materials for cleaning glassware were obtained and a device for washing rubber tubing under pressure was installed. At the same time it was possible to replace the narrow-neck plasma bottles in Chinese donor sets with wide-neck commercial solution flasks. The decrease in pyrogenic reactions was dramatic. In contrast to an incidence of 22.71% of chills and fever during July and August, 1944 only 4.5% of transfusions were complicated by these reactions during September and October, 1944. With further improvements in cleaning facilities and additional refinements in the cleaning technique it is believed that these reactions could be vir ually eliminated. The cleaning procedure used was similar to that which enabled Lewisohn and Rosenthal[6] to reduce pyrogenic reactions from 12% to 1%.

Three of the possible factors investigated in connection with the pyrogenic reactions proved to be of little, if any, significance. These were: (1) delayed refrigeration, (2) agitation of blood during transportation by truck, and (3) the open method of giving transfusions. The first two factors were eliminated by discontinuing the mobile blood procurement team and having the donors report to the hospital where the blood was immediately refrigerated without agitation. This was done at a time when reactions were frequent among Chinese patients, but the incidence of reactions was not reduced, in fact, it was higher following the change.

The open method was still in use after the incidence of reactions had been satisfactorily reduced by improvement in the cleaning technique, and it, therefore, seems reasonable to conclude that it had played little, if any, rôle in causing the reactions.

Comment. The blood transfusions herein reported have occupied a position of great importance among the therapeutic measures employed in this hospital. As has been found in other theaters of operations, whole blood is essential for the successful treatment of many battle casualties.

Although the danger of hemolytic reactions resulting from the iso-immunization of Rh negative individuals by repeated transfusions of Rh positive blood is well recognized, no such reaction has occurred in this series. In this regard the opinion of Simmons and Gentzkow[8] "that such reactions will not constitute a serious military problem" is of interest. In the Chinese, who are virtually 100% Rh positive,[5] this factor may probably be safely ignored. Rh antiserum (dried) has recently been received and its use in protecting American patients receiving multiple transfusions is planned.

The use of universal donors, condemned by many writers because of the danger of hemolysis resulting from the transfusion of incompatible isoagglutinins, has resulted in no hemolytic reactions in this series of transfusions in American patients. This corresponds with the experience of Harrison[2] in World War I and supports the opinion of Rosenthal and Vogel[7] that "one should not hesitate to recommend this practice for our own troops." Intragroup transfusions are, of course, to be preferred when possible.

Although not serious in any instance, the frequency of pyrogenic reactions for many months was troublesome, particularly in sick patients. Our experience with these reactions emphasizes the importance of meticulous cleansing of all blood transfusion paraphernalia.

Summary. 1. An analysis of 2350 blood transfusions given to Chinese and American troops at an Army General Hospital in India has been made.

2. Whole blood was used in larger quantities than liquid and dried human plasma in treating battle casualties.

3. Type B blood was found to be somewhat commoner in Chinese than in Americans.

4. Proteolytic reactions occurred more frequently than has been reported in the United States.

5. Use of the universal donor for American patients and multiple transfusions given without regard for the Rh factor resulted in no hemolytic reactions.

6. A high incidence of pyrogenic reactions due to inadequate facilities for cleaning transfusion apparatus was markedly reduced by institution of improved methods of removing pyrogens.

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A SIMPLE TECHNIQUE OF STERNAL MARROW BIOPSY FOR SPREADS AND SECTIONS

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There are two methods that are usually employed to obtain bone marrow from the sternum: the aspiration method and the trephine method. The aspiration method has the advantage that it can be performed with ease. It is a ward procedure which offers little discomfort to the patient and which can be repeated at frequent intervals. The disadvantage of this method is that while the films made from aspirated marrow are excellent for the study of cellular details, they do not permit an accurate estimation of the quantitative relationships of the cells nor do they allow a histopathologic study of the marrow structure.

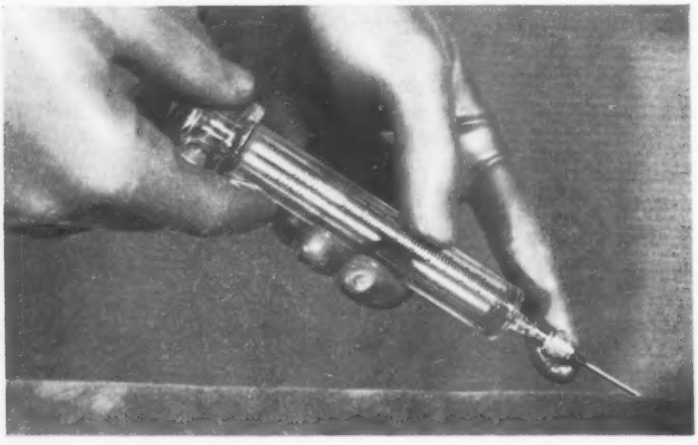

Fig. 1.—Position of syringe during aspiration of bone marrow.

The trephine method, on the other hand, has the advantage that it offers sufficient marrow tissue for a satisfactory histopathologic study. The disadvantage of this method is that it is a surgical procedure. It requires special equipment, necessitates an incision of the skin, and cannot be repeated at frequent intervals.

During the last year we have devised and used routinely a simple technique which not only combines most of the advantages of the aspiration and the trephine methods, but eliminates their disadvantages. Our technique resembles the usual aspiration technique in that we puncture the sternum and aspirate marrow tissue and blood. It differs from the usual aspiration method in that the blood is allowed

FIG. 2.—Position of syringe in which the specimen is allowed to clot.

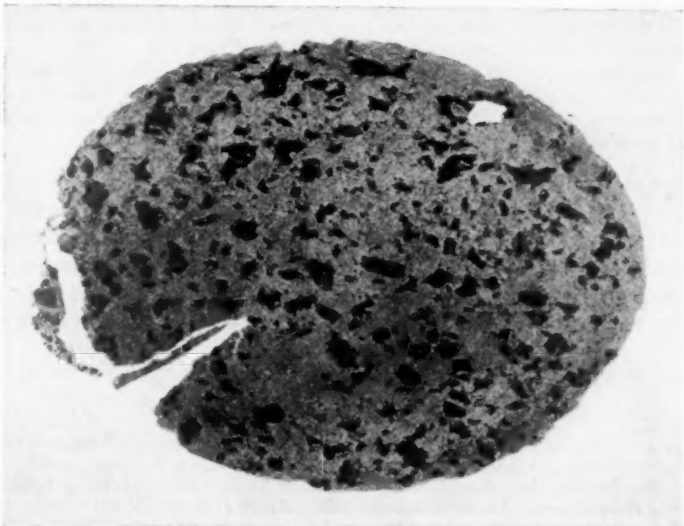

FIG. 3.—Complete section through the disk-shaped clot, from a patient with pernicious anemia. Note the numerous dark particles of marrow contained in the clot. Azure II Eosin, × 8.

to clot so that the tissue particles form a disk which without decalcification can be cut and stained as readily as any other tissue.

Technique. The site of puncture is a point determined by the mid-line of the sternum and a line through the level of the upper margin of the third costal cartilage. The skin over this and the surrounding area is prepared by shaving, cleaning and applying an antiseptic solution. The skin, subcutaneous tissue, and periosteum are then infiltrated with 1% novocaine. When anesthesia is complete, the needle, a 15 gauge Osgood sternal puncture needle, is inserted with the stylet in place, until the anterior lamella of the sternum is penetrated. When the tip of the needle has entered the marrow cavity the stylet is removed and with very gentle pressure and a slight rotatory motion the needle is forced into the marrow cavity at an angle of 30 to 40 degrees for a distance of not more than 7 mm. in an adult, or until the tip first meets the greatly increased resistance of the posterior lamella. A dry 10 cc. syringe is then attached and sternal marrow and blood are aspirated until the specimen reaches a depth of 2 or 3 mm. in the syringe. It should not be neglected to remove the stylet before the needle is forced through the marrow cavity so that its lumen gathers marrow tissue in passing. It is important that the capillary of the syringe tip should have a bore equal in diameter to that of the needle so that the marrow particles will meet no obstruction in passing from the lumen of the needle into the syringe.

As soon as the material has been obtained, the syringe is detached and the stylet returned to the needle in the sternum. The syringe is changed immediately from the horizontal position (Fig. 1) to a vertical one (Fig. 2) and the plunger is withdrawn until its distal end is approximately 1 cm. above the mouth of the syringe. The specimen is allowed to clot in this position. When it has clotted well, the plunger is removed completely and the specimen which adheres lightly to its distal end is dropped into freshly prepared Zenker's formol solution for fixation.

Inspection of the clotted specimen shows small gray or yellow particles which are either concentrated on one or the other surface of the clot or evenly dispersed within it depending upon the relative specific gravities of the marrow particles and the marrow blood. After fixation, the specimen is washed, dehydrated, cleared and embedded in paraffin in such a way that the greatest number of marrow particles are exposed for section. The sections are made and stained with Azure II Eosin by routine methods.

If films are desired, the needle is withdrawn until its tip is at the level of the anterior lamella, the stylet is then removed and the needle is reinserted into the marrow cavity as before, but in a slightly different direction. A second syringe is attached and a second specimen aspirated. When the syringe has been detached the stylet is reinserted and the sternal needle removed as a collodion dressing is applied.

Results. Some results obtained with our method are presented in Figures 3 to 6. Figure 3 shows a complete section through the disk-shaped clot; the particles of marrow appear dark in the illustration. Figure 4 shows comparatively few small particles of marrow, while Figure 5 represents a biopsy containing many large pieces. Figure 6, finally, represents a higher magnification of Figure 5; the latter shows

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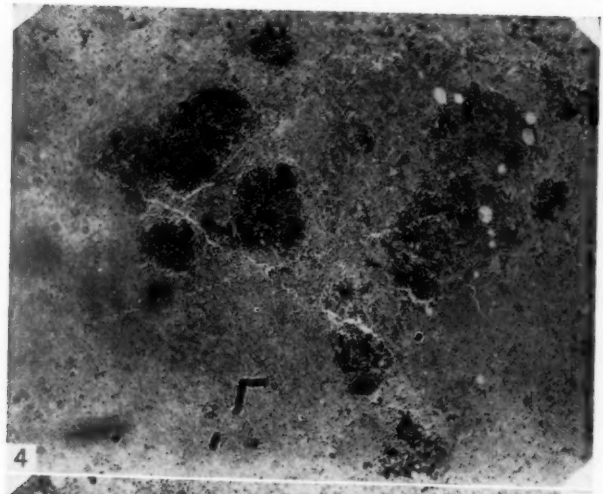
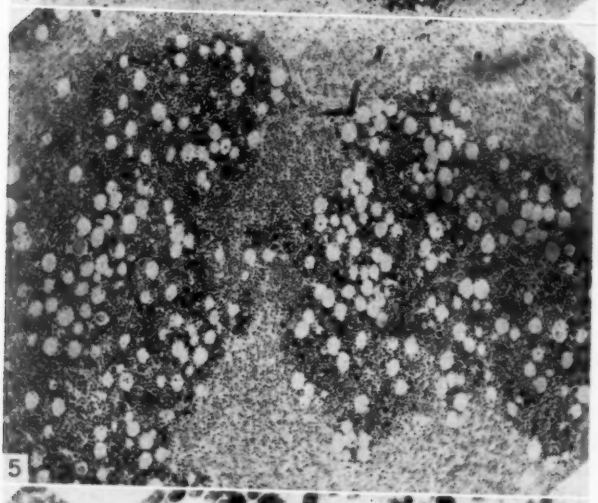
LEGENDS FOR FIGS. 4, 5 AND 6.

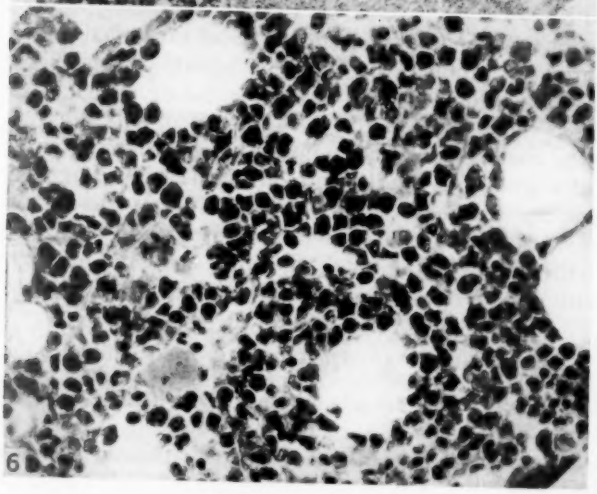
FIG. 4.—Section through clot containing comparatively few small marrow particles' from patient suffering from post-hemorrhagic anemia. Azure II Eosin, × 80.

FIG. 5.—Section through clot containing many large marrow particles, from patient suffering from subacute bacterial endocarditis. Azure II Eosin, × 80.

FIG. 6.—Same as Figure 5. × 640.







FIGS. 4, 5 and 6.

an inflammatory response in a patient with subacute bacterial endocarditis.

Summary. A simple technique of sternal marrow biopsy is described which combines the advantages of the aspiration and the trephine methods. Figures 3 to 6 show representative results obtained with this method.

THE EFFECT OF VITAMIN K_1 OXIDE UPON THE ANTICOAGULANT PROPERTIES OF DICUMAROL*

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Dicumarol [3-3′-methylenebis (4-hydroxycoumarin)] has been used as an anticoagulant in disease conditions in which diminished coagulability of the blood is desired.[1,2,3,4] The clinical usefulness of dicumarol is limited by the slow and difficult reversibility of the impaired blood coagulability as evidenced by a prolonged coagulation time.[5] The action of dicumarol may be contrasted with that of heparin after the injection of which the prolonged blood coagulation time may be brought at once to normal by the administration of suitable amounts of protamine.[6]

Overman, Stahmann and Link[7] were able to show an antagonistic action of the vitamin K-like substance 2-methyl-1, 4-naphthoquinone to dicumarol administered to rabbits. Shapiro[8] and Davidson and MacDonald[9] confirmed this in man, the latter authors using the oxide of vitamin K_1.

The amount of dicumarol used by these investigators was below that required to prolong the blood coagulation time significantly, although the prothrombin time was prolonged in all instances. Lucia and Aggeler[10] demonstrated the effectiveness of vitamin K_1 oxide in returning the coagulation time to normal in 1 patient given dicumarol in sufficient amounts to produce prolongation of the coagulation time. The present report is concerned with the effect of the administration of vitamin K_1 oxide upon the *blood coagulation time* of patients who had been given dicumarol in amounts sufficiently large and for a sufficiently long time to prolong the blood coagulation significantly above normal.

Methods. The venous blood coagulation time was measured in glass tubes at 37° C. by a modification[11] of the method of Lee and White[12] (normal values 6 to 12 minutes). The prothrombin time was measured by a modification[13] of Quick's method.[14] The thromboplastin used in this test clotted normal plasma in from 20 to 25 seconds.

* The expenses of this investigation were defrayed in part by a grant given "In recognition of Dr. Francis W. Peabody's Services to the Foundation," by the Ella Sachs Plotz Foundation.

Dicumarol* was administered orally in gelatin capsules. Vitamin K_1 oxide was given intravenously in an alcohol-water emulsion prepared by a modification[9] of the method of Seligman.[15]

Results. Eleven patients were given dicumarol orally in varying amounts. Four patients had evidence of thrombophlebitis, 1 with obstructive jaundice as well. The remaining 7 patients were convalescing from acute illnesses. Their ages were from 43 to 75 years.

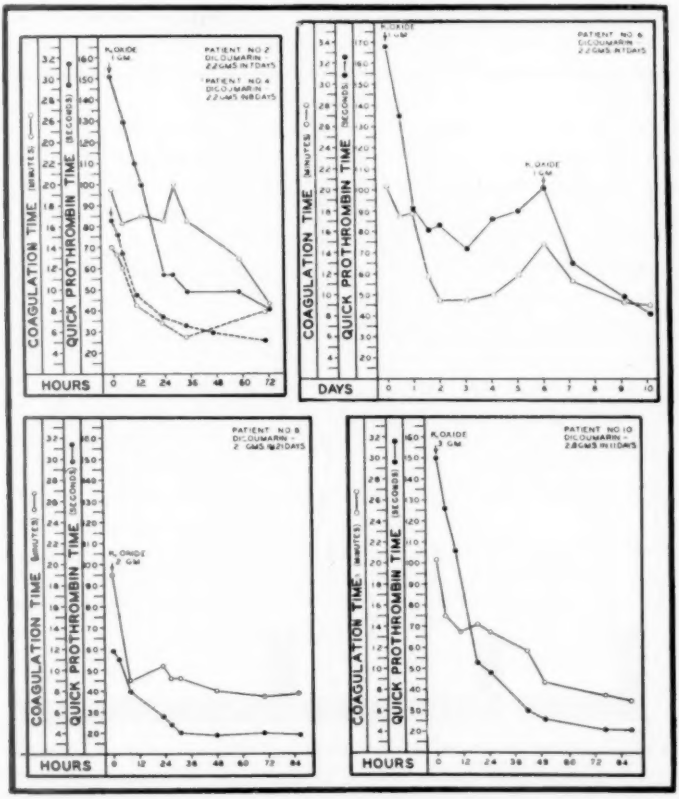
COAGULATION TIME (MINUTES)
QUICK PROTHROMBIN TIME (SECONDS)
HOURS
DAYS
K.OXIDE 1 GM.
PATIENT NO. 2 DICUMARIN 2.2 GMS. IN 7 DAYS
PATIENT NO. 4 DICUMARIN 2.2 GMS. IN 8 DAYS
PATIENT NO. 6 DICUMARIN 2.2 GMS. IN 7 DAYS
PATIENT NO. 8 DICUMARIN 2 GMS. IN 21 DAYS
PATIENT NO. 10 DICUMARIN 2.8 GMS. IN 11 DAYS

FIG. 1.—Antagonistic effect of vitamin K_1 oxide upon the anticoagulant effect of dicumarol in 5 patients.

From 3 to 21 days after the administration of from 1 to 3.6 gm. of dicumarol, the blood coagulation time, which had been within normal limits, became prolonged (over 12 minutes) in all 11 patients. The initial dose of dicumarol was from 0.5 to 1 gm., followed usually by a daily dose of 0.2 gm. One patient, No. 8, was given 0.8 gm. of dicumarol initially and thereafter the dosage was regulated to maintain his prothrombin time between 30 and 60 seconds. One patient, No. 11, after 8 days of therapy had a sudden and severe gastric hemorrhage and died before remedial therapeutic measures could be instituted. His coagulation time, the day of his death, was elevated to $18\frac{1}{2}$ minutes.

* Kindly furnished by the Abbott Laboratories, North Chicago, Ill.

To the remaining 10 patients from 0.5 to 3 gm. of vitamin K_1 oxide was given intravenously in from 1 to $2\frac{1}{2}$ hours. The blood coagulation time returned to normal in from $3\frac{1}{2}$ to 36 hours in each of these patients (Fig. 1).

Of the 10 patients given vitamin K_1 oxide, 3 (Nos. 1, 2 and 5) were given 0.2 gm. of dicumarol without interruption for 6, 8 and 12 days thereafter. The coagulation time remained normal in the patient to whom administration of the drug was continued for 2 days. The patient to whom administration was continued for 6 days (No. 5) had

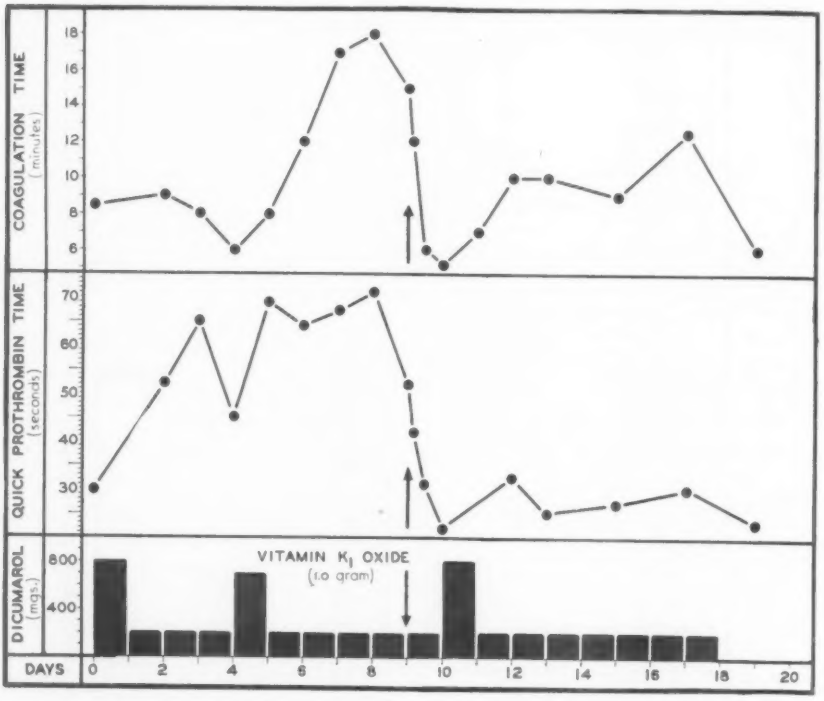

FIG. 2.—Antagonistic effect of vitamin K_1 oxide upon the anticoagulant effect of dicumarol in spite of continued administration of dicumarol.

a normal coagulation time for 5 days, but on the 6th day his coagulation time rose to 16 minutes. Patient 1 was given 0.2 gm. dicumarol daily for 8 days (Fig. 2) and was then given 1 gm. of vitamin K_1 oxide. On the next day he was given an additional 0.8 gm. of dicumarol, but in spite of this his coagulation time remained normal for the succeeding 8 days.

Discussion. The action of large amounts of vitamin K_1 oxide in reversing the hypoprothrombinemia induced by dicumarol is equally effective in reversing the prolonged coagulation time in the 10 patients reported here. This effect is seen even if the administration of dicu-

marol is continued after the vitamin K_1 oxide has been given. However, after the administration of vitamin K_1 oxide, normal blood coagulation times did not occur for from $3\frac{1}{2}$ to 36 hours. Thus the control of the abnormal blood coagulability is not rapid enough to prevent excessive loss of blood if brisk hemorrhage were to ensue. This is clearly illustrated in Patient 11 who died of hemorrhage. In his case had heparin been used instead of dicumarol it might have been possible by the use of protamine to bring his coagulation time to normal and stop the bleeding. Therefore, it seems evident that if a prolonged blood coagulation time is desired and dicumarol is used, control of the coagulation time must be sacrificed to a dangerous degree.

Clinical evidence is accumulating which suggests that at least to prevent phlebothrombosis postoperatively, doses of dicumarol small enough to prolong the prothrombin time, but not the coagulation time, may be effective.[16,17] If these reports are substantiated it may be that such a use may be an important contribution to therapeutics. Nevertheless, when reduced blood coagulability of a greater degree is desired as after vascular surgery, the lack of control using dicumarol, even with vitamin K, makes it an unsafe drug for use at present.

Summary. 1. The prolonged blood coagulation time following the ingestion of dicumarol was returned to normal in from $3\frac{1}{2}$ to 36 hours by the intravenous administration of large amounts of vitamin K_1 oxide in 10 patients.

2. This effect was evident in spite of the continued administration of dicumarol.

3. Following the administration of dicumarol 1 patient died of severe bleeding before control could be instituted.

4. The use of dicumarol in conditions requiring prolongation of the blood coagulation time is at present still dangerous because of lack of control.

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FINAL NOTE ON A REPORTED CASE OF ERYTHREMIA, GOUT AND SUBLEUKEMIC MYELOSIS

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In 1939 I reported in this journal a case of erythremia, gout, anemia and the blood smear and bone marrow characteristics of subleukemic myelosis in a female patient observed during a 5-year period.[4] The statement was made that "the subsequent course may determine the proper designation." In view of the fact that the further clinical course and autopsy findings of this patient are available, this subsequent report is presented.*

Subsequent Clinical Observations. After discharge from the hospital in April, 1938, the patient continued to show severe anemia, splenomegaly, considerable dyspnea, some pain in the lower sternum and slowly lost weight. In November, 1939 she was admitted to a hospital because of recurrence of a lesion on her nose, and persistent splenomegaly and anemia. Examination showed slight wasting, marked pallor, a small basal-cell carcinoma of the nasal tip, no palpable lymph nodes and a non-transmitted systolic murmur at the cardiac apex. The lower border of the spleen reached below the iliac crest, the right border extended at least 4.5 cm. beyond the umbilicus, and the spleen was described as "hard and rocky' and "projecting anteriorly in a manner not unlike pregnancy." There were many varicosities in the lower extremities and tophi palpable in the dorsum of the distal phalangeal joint of each first phalanx of the feet. Examination otherwise was not remarkable. At that time the erythrocytes were 2,800,000 per c.mm., hemoglobin 43%, and the leukocytes 7100 (45% neutrophils, 27% band cells, 1% eosinophils, 7% small lymphocytes, 1% "young monocytes," 8% neutrophilic myelocytes, 5% metamyelocytes, 2% "young cells," and 4% "stem cells"). Other studies showed icteric index 12.5, blood uric acid 12 mg., N.P.N. 27 mg. per 100 cc., and metabolic rate + 68.

The patient received blood transfusions but gradually became weaker. A splenic puncture showed what was described as "myeloid metaplasia." A sternal biopsy showed "a hyperactive marrow with megakaryocytes." She received 200 r high voltage Roentgen ray in divided doses directed to the anterior splenic area. In February, 1940 the erythrocytes were 2,460,000 per c.mm., hemoglobin 48%, and leukocytes 3800 per c.mm. There was no significant change in splenomegaly. The patient was discharged and died in March, 1940, approximately 8 years after she first noted a left abdominal mass.

Autopsy (significant features of gross findings). External examination showed marked pallor and slight icterus. There was no palpable lymphadenopathy. The subcutaneous tissues of the trunk were wasted and edematous. The *peritoneal cavity* contained approximately 200 cc. of clear straw-colored fluid. The right *pleural cavity* contained approximately 1200 cc. of clear straw-colored fluid, the left pleural cavity approximately 1000 cc. and the *pericardial cavity* approximately 50 cc. of similar fluid. The *heart* weighed 300 gm. and was greatly dilated. The myocardium was slightly paler and softer than usual. The *liver* (1800 gm.) was smooth and brownish and had

* I am indebted to Dr. S. C. Dalrymple, Newton, Mass., and Drs. Shields Warren and R. W. Rawson, Boston, whose kind coöperation has made available the subsequent clinical observations, gross autopsy findings and tissue for microscopic study.

an appearance suggestive of considerable hemosiderin deposition. Its edge was 4 fingerbreadths below the costal margin; the left lobe was 5 fingerbreadths below the ensiform cartilage, extending well into the left quadrant. The *spleen* (1290 gm.) was greatly enlarged, the anterior pole lying almost to the midline at the level of the umbilicus. Its capsule was smooth except for two small areas of infarction on its upper border. These areas measured approximately 2 cm. in diameter and were deep red and reddish gray in color. The remainder of the spleen was firm and reddish with innumerable irregular deeper red patches throughout. The left *kidney* weighed 100 gm., the right 120 gm. Cut surfaces appeared pale with slight cortical narrowing. The calices and pelves showed no dilation and contained brownish granular material. In the left kidney pelvis was a lima bean-sized stone of similar material measuring 2 cm. in length. Chemically it showed a nucleus of uric acid with an outside coating of uric acid and ammonium urate. The *ureters* were edematous but not dilated. The *mesentery* contained a few small scattered pea- and bean-sized nodes which were soft, white and grossly not remarkable. The portal, superior mesenteric and splenic *veins* were without evident lesion. Rib, vertebral and femoral *marrow* was deep red; that in the femur seemed gritty. The lungs, pancreas, adrenals, bladder, uterus, tubes, ovaries, thyroid, esophagus, stomach, small intestine and large intestine were without evident lesion except for slight edema of the wall of the gastro-intestinal tract.

Microscopic Findings. Sections of *spleen* showed an increased amount of pulp diffusely infiltrated with large numbers of early leukocytes of the myeloid series with scattered foci of nucleated red cells. The sinusoidal endothelium was prominent. "Germinal centers" were preserved but less frequent than usual. The *liver* sinusoids contained less prominent foci of myeloid cells with some myelocytes, metamyelocytes and young neutrophils. Sections of *bone marrow* from various sites showed marked diffuse cellularity, mainly marked erythrogenic hematopoiesis with frequent foci of myeloid hematopoiesis. Megakaryocytes were numerous. Sections of other organs showed no significant findings.

The final *diagnoses* were: extramedullary hematopoiesis of the spleen (marked) and liver (moderate); marked splenomegaly; hyperplasia of the bone marrow; anemia; edema, hydrothorax, slight ascites and slight hydropericardium; cardiac dilation; splenic infarction; and uric acid calculus of the left kidney pelvis.

Comment. Myeloid metaplasia of the spleen has come to be recognized as a fairly frequent condition which may mimic various blood dyscrasias. The clinical features and autopsy findings of this case parallel those described as "agnogenic myeloid metaplasia of the spleen" by Jackson, Parker and Lemon.[1] A long series of experiments dealing with benzol (benzene) poisoning in the rabbit, carried on by Weiskotten and his associates,[6–9] has not showed a comparable degree of hematopoiesis in the rabbit spleen. However, toxicologic investigations[2,3] indicate that myeloid metaplasia of the human spleen frequently is associated with chronic benzol* poisoning. Opinion has been expressed that a relationship between myeloid metaplasia and leukemia cannot be excluded.[2,5] Several other cases of myeloid metaplasia of the spleen studied in this department have presented similar autopsy findings and clinical courses easily confused with leukemia or various types of anemia. One of these cases had a history of exposure to a compound related to benzol. In the case reported, I know of no history of chronic exposure to benzol. The patient

* The term "benzol" is used here in the sense of its usage by Mallory, Gall and Brickley,[2] to mean the ordinary commercial benzol rather than the chemically pure product (benzene).

received Fowler's solution during her initial polycythemic phase and radiation over the splenic area terminally.

Summary. Through 8 years, this patient had successively splenomegaly, erythremia, anemia, and blood smear and bone marrow characteristics of so-called subleukemic myelosis. At autopsy, extensive myeloid hematopoiesis of the spleen, moderate myeloid hematopoiesis of the liver, and bone marrow hyperplasia, particularly erythrogenic, were found. It was thought that these features perhaps represent successive stages of a single hematopoietic disorder of unknown etiology. Conditions associated with splenic myeloid metaplasia, such as chronic benzol exposure, are discussed. Gout was regarded as probably a coincidental feature.

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PERIARTERITIS NODOSA
A Case With Autopsy

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Periarteritis nodosa is a relatively rare disease, described first by Kussmaul and Meier in 1866, and characterized pathologically by panarteritis of the medium-sized and small arteries throughout the body. The clinical symptoms, which are protean, depend upon the system which is the most affected in the development of the disease. The etiology is not definitely known, but the pathologic findings of polymorphonuclear and round cell infiltration in the adventitia and media of the affected vessels point toward an infectious basis. Recently Rich and Gregory have pointed out the rôle of hypersensitivity in the etiology of the condition.

The following case is reported because of its occurrence with rapidly fatal manifestations in a previously healthy young soldier who did not break down until after the stress of combat.

Case Report. A 21 year old artillery private, native of Washington, D. C., reported to his battalion surgeon on June 25, 1944, in France, complaining of abdominal pain and nausea, of a few hours duration. The patient had a fever

of 100° F. (37.8° C.). A diagnosis of acute appendicitis was made and the patient was evacuated to a clearing station. Operation was not performed and the patient was sent through the chain of evacuation to the United Kingdom, arriving at this hospital on July 6, 1944. The past history revealed nothing of significance except seasonal hay fever. The patient's complaints, 11 days after the onset of the initial symptoms, consisted of moderate pain in the upper right quadrant, moderate weakness, and anorexia. Physical examination revealed moderate emaciation, fever of 99.5° F. (37.5° C.), tenderness and a rather indefinite, deep, firm mass in the upper right quadrant of the abdomen, extending from the epigastrium to the right flank and 10 cm. below the costal margin. The heart and lungs were not remarkable. There was no lymphadenopathy nor edema of the extremities. Rectal examination revealed no abnormalities in the anus or lower rectum. The blood pressure was 138/84. The skin was normal.

Laboratory Studies. Roentgen studies of the chest, stomach, duodenum and colon revealed nothing remarkable. Proctoscopic examination revealed no ulcerations, polyps, or tumors in the descending colon. Stool examination and culture revealed no parasites or ova. A blood count on July 8 revealed the following: RBC 3,330,000, WBC 14,650 (neutrophils 88%, lymphocytes 12%), Hb 76% (11 gm.) (Sahli). Urine examination revealed normal findings.

In view of the secondary anemia blood transfusions of 500 cc. of compatible bank blood were given on July 13 and 15. In spite of the transfusions, blood studies on July 15, 1944, revealed RBC 3,120,000, Hb 70%, WBC 15,100 (neutrophils 90%, lymphocytes 10%).

The patient continued to complain of pain in the abdomen and did not improve under medical measures. On July 15, 1944, a laparotomy was performed, preceded by a transfusion of 500 cc. of compatible bank blood, and alkalinization by means of sodium lactate. The tentative diagnosis before operation was subacute perforation of a duodenal ulcer or acute suppurative cholecystitis. Under gas-oxygen-ether anesthesia, with upper right rectus incision the following lesions were noted: the liver was markedly enlarged, the inferior margins rounded, extending 10 cm. below the costal margin. The enlargement involved all lobes and the palpable mass before operation was found to be the quadrate lobe. The capsule was smooth, glistening, and did not appear cirrhotic. The color was mottled red-brown, and darker than normal. There were numerous dense, fibrous adhesions between the dome of the right lobe and the diaphragm. The spleen was slightly enlarged, of normal consistency, and the margins rounded. The stomach, duodenum, kidneys, entire small and large intestine and appendix appeared normal. The mesentery and retroperitoneal lymph nodes showed no pathologic changes. The omentum was delivered from beneath the liver margin with difficulty after freeing pericholecystic adhesions. The gall bladder was moderately enlarged, thick-walled and the peritoneal surface was gray-white in color. The wall was edematous throughout and free from any evidence of gangrene or perforation. No calculi were palpated in the cystic or common ducts. In view of the obviously pathologic changes in the gall bladder, it was felt that the liver changes might be secondary to acute suppurative cholecystitis and cholecystectomy was carried out. Examination of the gall bladder after removal revealed a large thrombotic area situated intramurally in the posterior aspect opposite the ampulla. Gross section revealed no evidence of calculi, but the mucosa was of "strawberry" appearance with no evidence of necrosis. The wound was closed in layers and Penrose drainage was instituted from the foramen of Winslow. The patient evidenced mild shock postoperatively and whole blood was given during and immediately after the operation.

The postoperative convalescence was uneventful until the 7th day. The patient's temperature was normal 2 days after operation, pulse and respirations were normal, his appetite returned and he was anxious to get out of bed. On the 7th night the patient suddenly became dyspneic and orthopneic. Cyanosis was noted, and the superficial veins of the forehead and neck became engorged. Physical examination disclosed coarse râles and rhonchi throughout both lung

fields with dullness in both bases. The cardiac borders were slightly widened both to the right and left. The heart rate was rapid, the apex rate being 160. Blood pressure was 160/100. There was gallop rhythm. A roentgenogram of the chest next morning disclosed dilation of the right auricle and ventricle and marked passive congestion of both lungs. Rapid digitalization was carried out, oxygen therapy was instituted, and the usual treatment for cardiac failure given. Examination of the abdomen showed the operative wound to be intact and not infected. The liver border was palpated 8 cm. below the costal margin. The patient held his own on 8th day, the pulse rate dropping to 108, but the gallop rhythm persisted. There was marked diminution of râles in the lungs, and it was felt that he might survive. Next day the patient was brighter, the pulse was 100, gallop rhythm still present. An electrocardiogram disclosed changes characteristic of myocardial failure. The NPN of the blood was 60 mg./100 cc. of blood. At 1715 hours on the ninth postoperative day, while talking to a ward attendant who was feeding him, the patient suddenly expired.

Autopsy (2 hours after death). Only the significant findings are presented.

Heart. The epicardial surfaces were smooth and glistening. The right auricle was dilated to approximately 4 times normal size. The tricuspid valve was competent and there were no scars or vegetations present. The right ventricle was slightly dilated and the wall thickened slightly. The pulmonary valves were competent and the endocardial surfaces smooth. The endocardial surface of the right auricle was smooth and glistening. There were a few postmortem thrombi on the right ventricular wall. The left auricle was normal in size and appearance. The foramen ovale is closed. The left ventricle was normal in size and the endocardial surfaces smooth and glistening. The mitral valve was normal. There were a few small yellow plaques of atheroma in the region of the aortic ring. The aortic valves were normal. Cut surfaces through the interventricular septum and through the walls of the ventricles revealed a reddish gray surface, which was lighter in color than normal. The coronary arteries were grossly thickened on section and there were a few thrombi present in the anterior descending branch of the left coronary artery.

Lungs. Both lungs were edematous and boggy. There were no thrombi in the pulmonary vessels and the bronchi and bronchioles appear normal. In the left lower lobe, inferior surface, there was an area of recent hemorrhage measuring approximately 2 by 2 cm. No thrombus could be demonstrated in the efferent or afferent blood-vessels to this area.

Liver. The liver was markedly enlarged, rather soft in consistency, and the superior surface of the right lobe is adherent to the diaphragm by dense fibrous adhesions. The markedly enlarged left lobe was adherent to the spleen and the gastro-colic omentum by firm fibrous adhesions. The omentum was densely adherent to the gall bladder bed and to the inferior surface of the right and left hepatic lobes. When the liver was removed from the peritoneal cavity there were many areas of dense fibrous tissue radiating from foci of scarring in the capsule. Cut surfaces of the scarred areas in the capsule disclosed multiple round and oval-shaped areas of necrosis surrounded by definite capsules. These areas measured from 3 by 3 cm. to tiny areas of a few mm. in diameter. Most of the infarcts were subcapsular and were scattered throughout both right and left lobes. Branches of the hepatic and portal blood-vessels throughout the liver were thickened and in the left lobe there were well-organized thrombi in the largest branches of the portal vein. The intervening liver tissue between the necrotic areas appears essentially normal on examination.

Spleen. The spleen appeared normal in size and texture. Near the lower pole there were a few fibrous adhesions to surrounding structures. The cut surfaces revealed a dark red, rather firm parenchyma. There were no infarcts or necrotic areas in the spleen, nor evidence of hyperplasia of the pulp.

Pancreas. This organ appeared normal in size and color, but felt slightly more firm than normally. The splenic vessels were patent throughout.

Adrenal Glands. The right adrenal was markedly thinned-out and adherent by fibrous adhesions to the inferior aspect of the enlarged right lobe of the liver. No medullary tissue was present grossly and the cortex was approximately 1 mm. in thickness. The left adrenal appeared normal in size and texture and the cortical and medullary markings were well preserved.

Kidneys. The right kidney was smaller than normal. The perirenal fat was minimal and there were old scars on the capsule of the kidney. The kidney appears pale and softer in consistency than normal. The capsule stripped with difficulty and was adherent to the cortex by adhesions over the areas of scarring. Surfaces made by cutting revealed a gray cortex, narrower than normal, and in which there were multiple triangular-shaped areas of necrosis. The bases of the triangles were subcapsular while the apices were directed toward the pelvis. These areas varied in size from 2 to 4 mm. in their greatest extent. The medullary portion of this kidney was streaked with gray fibrotic laminæ radiating from the pelvis. The pelvis is normal in size and studded with pin-point hemorrhages in the mucosa. The ureter was normal. The left kidney resembled the right and contained multiple subcapsular necrotic areas which produced scarring of the overlying capsule.

The *gastro-intestinal tract* appeared normal throughout.

The *inferior vena cava*, mesenteric vessels, and those branches of the portal system below the hepatic portion were patent throughout their walls and did not appear thickened.

MICROSCOPIC EXAMINATION (by Lt. Col. D. Murray Angevine, Medical Corps, A.U.S.).

Lung. The bronchioles are patent and slightly collapsed. The alveolar septa are moderately thickened by hyperemia and edema with considerable swelling of the epithelium. Most alveoli are filled with edematous fluid; many are filled by a hyaline-like membrane. In one section an extensive fresh intra-alveolar hemorrhage is seen, with a few adjacent alveoli filled by partly organized fibrin coagulum. Several small vessels contain unattached thrombi.

Heart. The subepicardial fat was extensively infiltrated with round cells. In the myocardium numerous slightly degenerated muscle cells are seen. Adjacent to several small branches of the coronary artery, the muscle cells are considerably degenerated with a slight round cell infiltration and vascularization of the interstitial tissue. In a large branch of the coronary artery the lumen is partly occluded by a recent thrombus, adherent to an eccentrically thickened hyalinized slightly degenerated intima containing considerable fresh hemorrhage. The adventitia and outer fringe of media is extensively vascularized and moderately infiltrated with round cells, plasma cells and a few eosinophils.

Liver. In one section is seen a large vessel completely filled by a laminated compact adherent thrombus, with organization of the periphery. The media and adventitia are moderately vascularized and slightly infiltrated with round cells. There is considerable centrilobular congestion and parenchymal degeneration in the adjacent tissue. A similarly affected vessel, with more extensive vascularization is observed in a second section, with an extensive centrilobular necrosis, containing many pigment-laden histiocytes.

Gall Bladder. The epithelium is extensively desquamated. In the fibromuscular layer the adventitia of every artery is considerably thickened by an extensive infiltration of eosinophils, leukocytes, monocytes and round cells and with moderate vascularization. In several vessels, the intima is slightly thickened, and the endothelial cells are distended and ballooned by intracytoplasmic perinuclear vacuoles.

Cystic Artery. One large and several smaller branches of the artery are observed, joined together by a granular-like tissue continuous with the thickened vascularized adventitia, and extensively infiltrated with eosinophils, and round cells. The large and few small branches are filled with thrombi. The intima is considerably thickened and vascularized in a few small vessels.

Pancreas. Numerous arteries are thickened and infiltrated similarly to those described in the liver and gall bladder. In a few small arteries the lumen is nearly occluded by a thickened intima.

Adrenal. In the periadrenal adipose tissue, several arteries are conspicuously thickened by a vascularized fibrosed adventitia and a greatly thickened hyalinized intima.

Kidney. In one section an area of coagulation necrosis is observed in the cortex adjacent to the capsule. The adventitia of the interlobular arteries is infiltrated with round cells and vascularized. In many the intima is thickened and the lumen narrowed. An interlobular artery is filled with a recent thrombus.

Comment. (Lt. Col. Angevine). "The extensive visceral vascular lesions, confined to the medium-sized arteries and affecting mainly the adventitia, indicate that this is a case of periarteritis nodosa. The almost complete involvement of the gall bladder vessels is an interesting finding in relation to the clinical history of suspected cholecystitis. The vascularity and extensive inflammatory exudate with moderate fibrosis are consistent with an early stage of the disease. The case will be coded as: periarteritis nodosa, early."

Summary. A fatal case of periarteritis nodosa with vascular lesions in several viscera has been presented. Nothing was brought to light as to the etiology. The history of hay fever might be significant in view of the recent work of Rich and Gregory. The remarkable feature of this case is the absence of symptoms until shortly before the final illness.

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CALCIFIC AORTIC VALVULAR STENOSIS

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The purpose of this communication is to report the occurrence of an unexpectedly large number of instances of calcific aortic stenosis among autopsies at a U. S. Marine Hospital, to present significant data concerning this condition, and to attempt an etiologic subdivision of the cases.

After a period of service, the author became aware of the strikingly increased incidence of deformities of the aortic valve in the material at this hospital compared with that seen in private and municipal hospitals. The material forming the basis of this paper—31 examples of fibro-calcific deformities of the aortic valve—was derived from 500 consecutive autopsies. Hall and Ichioka[1] also described 31 cases of the same type, but their autopsy volume is estimated at 4000 or more. Reich[2] reported 22 examples of aortic deformity with calcification (cases of mitral stenosis were excluded) derived from 8 years' postmortem material at Kings County Hospital, a total of about 10,000 autopsies. No explanation is offered for the heightened frequency of the condition at the Marine Hospital; but factors of age, sex and occu-

TABLE 1.—CASES OF CALCIFIC AORTIC VALVULAR STENOSIS WITH PREDOMINANT RHEUMATIC PATHOLOGY

No.	Age	Race	Hist. of RF	Heart wt.	Anatomy of aortic valve	Histology of aortic valve	Other heart lesions	Other disease
806	45	Eng.	Yes	380	Cusps thick, edges rolled; adherent commissures; nodular calcification on margins	Spongiosa vascularized; hyaline scars and calcification in ventricularis	Aschoff bodies	Fracture of skull
838	43	U. S.	Yes	650	Cusps short and fused; rolled calcific edges and thick bands between cusps	Fibrinoid foci, vascular spongiosa with exudation	Mitral stenosis	
834	48	U. S.	Yes	800	Bicuspid deformity; thick cusp margins; calcified commissure	Hyaline scars in ventricularis; vascularization and calcification in spongiosa.	Mitral stenosis	Multiple infarcts
852	39	Ital.	Yes	680	Short adherent cusps, rolled edges, calcification in margins and bases.	Fibrinoid degeneration and hyaline scarring of spongiosa and ventricularis; new vessels and Aschoff bodies	Mitral stenosis	Multiple infarcts
860	47	U. S.	Yes	750	Calcified adherent cusps; nodular margins; warty masses on both surfaces	Vascularized spongiosa and hyaline scarred ventricularis; focal lymphocytes	Sl. mitral nodularity	Adv. arteriosclerosis
875	62	U. S.	No	1000	Short calcified cusps, adherent to aortic wall	New vessels and focal scars in aortic ring; perivascular mononuclears in spongiosa	Pericard. adhesions; mitral st.	
907	45	Span.	No	470	Fused and calcified cusps, rough nodular margins; fresh vegetations (monilia)	Hyaline vascularized ring; focal scars beneath ventricular surface	Old pericarditis	
1222	34	Negro	Yes	975	Short calcified cusps; thick nodular closure line, fusion of two cusps	Dense hyaline necrotic foci, vascularized ventricularis, perivascular exudate	Focal scars of myocard.	
956	44	U. S.	Yes	850	Cusps and ring form a rigid triangular opening; aortic and ventricular surfaces rough and calcified	Calcification in hyaline scar tissue; new vessels and lymphocytes present	Mitral stenosis; pericarditis	Pulmonary infarcts
1016	35	U. S.	Yes	750	Cusps short and adherent; calcification on ventricular surfaces	Ventricular hyaline with fibrinoid foci; new vessels and mononuclear infiltration	Sl. mitral nodularity; Aschoff bodies	
1057	56	U. S.	No	600	Rolled edges, adherent commissures, with calcification at closure line	Subendocardial hyaline and fibrinoid degeneration; vascularization and mononuclear exudation	Sl. mitral thickening and narrowing	
1080	39	Norw.	Yes	900	Fusion of cusps by thick calcified commissures; edges rolled and nodular	Hyaline scars in ring and spongiosa; monocytes in perivascular foci	Mitral stenosis	
1092	67	U. S.	No	600	Bicuspid, with thick margins and calcification in sinuses; nodular and calcified mass on ventricularis of one cusp	Vascularization and perivascular mononuclear foci in spongiosa; hyaline scarring of ventricularis	Moderate mitra deformity	Cancer of bladder
1126	40	U. S.	Yes	610	Short cusps, calcified commissure, thick rolled margins	Hyalinized, fibrinoid foci in ring and cusps; new vessels and exudate in both spongiosa and ventricularis	Mitr. stenosis and pericarditis; Aschoff bodies	
1138	53	U. S.	Yes	900	Short cusps with calcified nodular ridge on ventricular surface	Aschoff bodies in spongiosa and fibrinoid subendocardial foci in ventricularis	Moderate mitral stenosis	
1158	49	Russ.	Yes	410	Cusps short and adherent; thick nodular margins; calcified masses in sinuses	Hyaline scars in ventricularis and spongiosa; foci of perivascular exudate	Mitral stenosis	
1167	47	U. S.	Yes	500	Bicuspid, nodular and calcified thick commissure; calcific masses in sinuses	Hyaline scars and calcification in ventricularis and vascularization and focal exudate in spongiosa	Mitral stenosis; Aschoff bodies	

TABLE 2.—CASES OF CALCIFIC AORTIC STENOSIS WITH PREDOMINANT PATHOLOGY OF MÖNCKEBERG'S SCLEROSIS

No.	Age	Race	Hist. of RF	Heart wt.	Anatomy of aortic valve	Histology of aortic valve	Other heart lesions	Other disease
853	63	Germ.	No	700	Cusps rigid with calcification in sinuses and smooth closure lines	Atheroma and fibrosis in fibrosa; no vascularization	Interstitial scars	Glomerulonephritis
859	66	U. S.	Yes	780	Calcification of ring and cusps; calcific masses in sinuses	Scars and focal calcification in ring and fibrosa of valve; no exudate; spongiosa normal	Mod. mitral deformity	Cancer of lung
904	43	Swed.	No	810	Cusps fused and covered on aortic aspect by spiky calcareous masses	Fibrosis, calcification and osseous metaplasia in fibrosa of cusps and ring	Myocardial fibrosis	Situs inversus
914	74	Swed.	No	450	Calcification and shortening of cusps; nodular masses in sinuses	Lipoid and calcific changes in aortic wall and fibrosa of cusps; no exudate	None	Meningitis
958	51	U. S.	No	775	Calcification of proximal halves of cusps and aortic ring	Atheroma and calcification of intima and fibrosa; atrophy of spongiosa; no exudate	None	Uremia
980	76	U. S.	Yes	530	Calcific masses on both sides of cusps; fusion of commissures; calcified ring	Intimal degeneration and focal calcification; fibrosa involved; no vascularization	Myomalacia; coronary sclerosis	
997	53	U. S.	No	600	Calcified nodular commissure with masses in sinus; rigid calcific cusps	Hyaline fibrosis and calcification in fibrosa and ring; no vascularization or exudate	Myocard. scars	Diabetes
999	50	Norw.	No	260	Atheromatous and calcific mass on commissure	Intimal degeneration and lipoid deposit; focal calcification; no vascularization	None	Ca. bladder; uremia
1027	43	U. S.	No	410	Calcific nodule on sinus surface of a commissure; cusp margins smooth and sharp	Intimal atheroma with foci of calcification in fibrosa; no new vessels or exudate	None	Fracture of spine
1071	68	Norw.	No	720	Nodular calcification on commissures, fusion of cusps; margins and edges smooth	Atheroma and calcification in aortic intima and fibrosa of cusps; spongiosa neg.	None	
1144	70	Swed.	No	410	Calcified plaques in sinus extending onto aortic surfaces of cusps	Atheroma of aortic intima; fibrosis in stroma of cusps; no vascularization or exudate	None	Diabetes
1227	78	U. S.	No	470	Calcified fused commissure with nodular masses in sinus; thin cusp edges	Atheroma and calcification in aortic intima and fibrosa of cusps; no vascularization	None	Cancer of mouth
1243	49	Negro	Yes	750	Cusps rigid and adherent to aortic wall; calcification on aortic aspect in sinuses	Atheroma, hyaline fibrosis and calcification in fibrosa; no vascular or perivascular lesions	Mitral thickening	Syphilis
1271	51	Negro	No	400	Atheroma and plaques of calcification on aortic side of cusps; thick fused commissure	Aortic intima and fibrosa of cusps show hyaline foci atheroma and calcification	None	Cancer of lung

pation are suspected. Our patients are predominantly male adults and a high proportion are seamen. Scandinavians are much more numerous than in the population at large. The average age of our deceased patients is 49 years.

TABLE 3.—ANALYSIS AND INCIDENCE OF CALCIFIC AORTIC STENOSIS IN 500 AUTOPSIES

Total valvular heart diseases	57
Cases of calcific aortic stenosis	31
Number of these showing mitral endocarditis	17
Etiology of calcific aortic stenosis by pathologic criteria:	
Entirely or predominantly rheumatic	17
Associated with severe arteriosclerosis	1
Entirely or predominantly atherosclerotic	14
Associated with diabetes	2
Associated with rheumatic lesions	2

The inclusion with our cases of instances in which other valves besides the aortic were diseased was decided upon because the two principal etiologic bases are rheumatic fever and arteriosclerosis. Since in the age group under consideration both of these diseases are frequent, it was obvious that all examples of aortic stenosis should be included, both with and without involvement of other valves by the same or another process. In these 500 autopsies there were found 57 hearts with valvular diseases, excluding only the characteristic aortic deformity associated with luetic aortitis. Of these cases, 40 showed varying degrees of mitral stenosis, and 31, including some of the mitral stenosis cases, showed calcific aortic stenosis. A further analysis of the types of aortic valvular damage is made in Tables 1 and 2, and a summary of the conditions found and their association with one another appears in Table 3.

After tabulating the cases and enumerating the anatomic and histopathologic details in each, it became apparent that a decision was required concerning the significance of several of the observations before a pathogenetic classification could be accomplished. Hall and Anderson[3] and Karsner[4] have reported that a majority of all hearts show typical rheumatic lesions if carefully examined for them. Therefore it has seemed to us that the use of rheumatic stigmata of the pericardium, myocardium and other cardiac valves as a basis for deciding upon the etiology of calcific aortic stenosis is unreliable. A better way to determine the rheumatic etiology of aortic valve lesions is to find the specific anatomic and histopathologic changes in the cusps and ring of the aortic valve itself. On this basis the 17 cases in Table 1 have been classified as rheumatic and the 14 cases in Table 2 as sclerotic.

The lesions included in Table 1 are variable in severity, reducing the aortic orifice moderately or severely. In some there are flat calcific plaques in the sinuses of Valsalva, thickening and stiffening the aortic cusps. In others this is combined with massive calcific nodules, or spiky encrustations on both aortic and ventricular surfaces of the cusps, sometimes with erosion of the intima and deposition of

fibrin thrombi. Fusion of the cusps is of variable severity, and results in the formation of a dense triangular diaphragm or a false bicuspid

FIG. 1.—Case 1092. Classified as rheumatic in etiology because of the bicuspid type of deformity, with thick rolled cusp margins (seen where the clamp is attached) and the histologic pathology. Moderate mitral valve deformity is present.

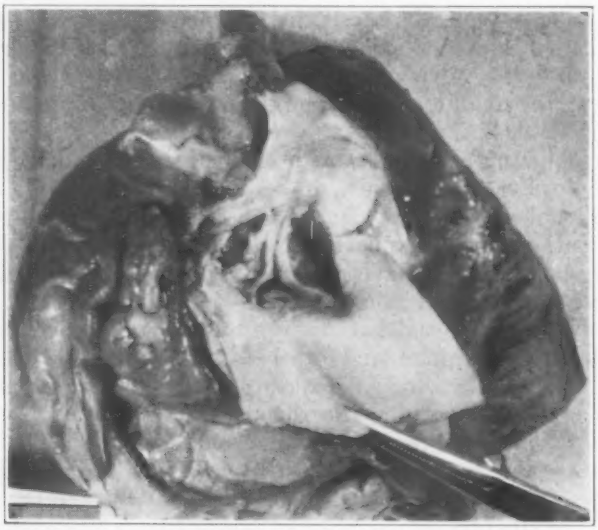

FIG. 2.—Case 956. Nodular calcification of all aortic cusps with the formation of a rigid funnel-shaped orifice. This heart showed mitral stenosis and histologic evidence of old rheumatic inflammation.

valve. The commissural lesions are broad and dense. The margins of the cusps and the closure line are least affected. Histologically the intima of the sinuses and cusps is thickened by edema and fibrillary

reduplication, with deposition of lipoid material in the subendothelial tissue. Phagocytosis of the lipoid occurs in plaques. The fibrosa of the cusps near their base becomes thickened and hyalinized. Foci of

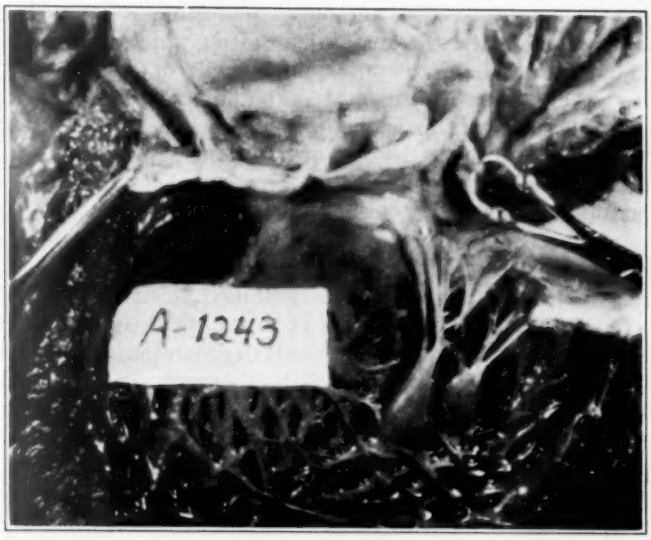

FIG. 3.—Case 1243. The cusps are rigid and partly fused by dense fibrosis in the commissures. Luetic aortitis is present but the histologic studies show that the valve deformity is sclerocalcific (Mönckeberg's type).

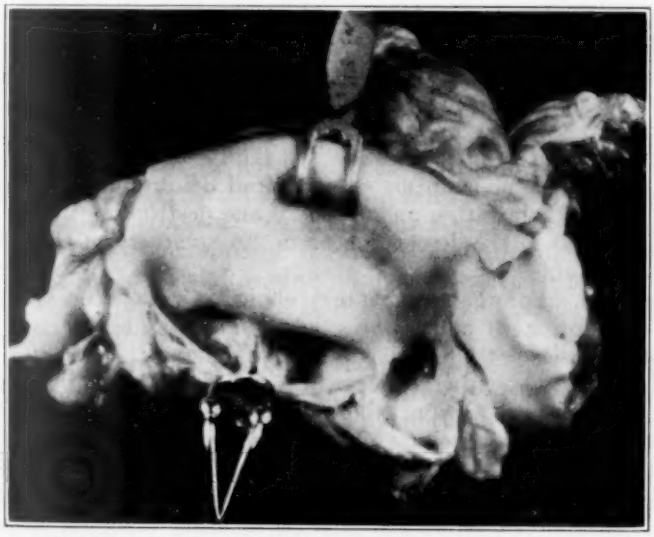

FIG. 4.—(This case is not in the series because there is no stenosis.) The early sclerotic and focally calcific thickening and degeneration seen at the cusp attachments to the aortic wall are regarded as the beginnings of Mönckeberg's sclerosis and are presented for comparison.

calcification occur in this layer and in the adjacent aortic ring. Osseous metaplasia is observed in some advanced lesions. The calcific masses impinge upon and may ulcerate through the ventricularis or arterialis of the valve. The spongiosa at the attachment of the cusp is usually narrow and shows few vessels and only a scattering of lymphocytes.

In Table 2 are listed the aortic deformities which in our judgment have the gross and microscopic appearances of rheumatic lesions. Many of them show considerable atheromatous degeneration and sclerosis superimposed upon the primary process. Although again there is wide variation in degrees of deformity, the usual lesion consists of shortening and thickening of the cusps in their distal portions, with nodularity along the closure line. The margins are rolled or inverted. The commissures are bridged by light fibrous bands. Bicuspid deformity is produced by intimate fusion of adjacent cusps, leaving a low fibrous ridge in the combined sinus of Valsalva thus formed. The histopathology is that of rheumatic fever. The principal features are Aschoff bodies, fibrinoid degeneration (with material present taking fibrin stains), arteriolar necrosis or disorganization, peri-capillary or peri-arteriolar exudation of lymphocytes and cardiac histocytes, and focal hyaline acellular scars. The sub-endocardial layer of the ventricular surface of the cusps and the spongiosa at the base of the cusps are characteristically the sites most involved.

The age incidence in the two groups is in a range from 43 to 78 years in the sclerotic, and 34 to 67 in the rheumatic cases. All were males. A history of an illness or symptom of the types generally recognized as associated with rheumatic infection was obtained in 13 of the 17 cases grouped as rheumatic on anatomico-histologic grounds, and in 3 of the 14 cases in which the aortic deformity was classified as sclerotic.

Disease of the pericardium, myocardium or valves other than the aortic was found in a considerable number of the cases. The chief coincidence was that of mitral stenosis. Ten of the 17 rheumatic aortic cases showed mitral stenosis. Of the 14 sclerotic aortic stenoses, 2 hearts showed moderate or severe mitral deformity, and 1 showed luetic type of infiltration and elastic tissue destruction in the aortic root as well as in the descending aorta. A summary of these figures appears in Table 3.

Discussion. For the past century clinicians and pathologists have been attempting to affirm the etiology and pathogenesis of fibrocalcific stenosis of the aortic valve, beginning with Hasse in 1846,[5] who believed that either endocarditis or atheromatous degeneration could be responsible. Mönckeberg[6] in 1904 described a type of aortic stenosis which be believed was due to primary sclero-calcific degeneration, beginning as plaques in the sinus pockets and ascending toward the free border of the valve cusps. The primary histopathologic lesion was described as sclerosis and calcification of the fibrous matrix of the valve. Further descriptions of calcific aortic stenosis of this type were given by Libman[7] and Ribbert.[8]

A number of modern authorities believe that rheumatic infection

is the principal, if not the exclusive, cause of aortic valvular deformities resulting in calcification and stenosis. Christian[9] described 21 cases in which the aortic valve alone was diseased and decided that the great frequency of a history of rheumatic manifestations (13 of the 21 cases) was significant and that "the etiologic relation of this lesion to rheumatic fever is very probable." Clawson, Noble and Lufkin[10] favor a rheumatic etiology for aortic stenosis in all cases as a result of a pathologic study of their material. Dry and Willius[11] came to the same conclusion on clinical grounds after studying a large series of cases, and offered the opinion that in calcific aortic stenosis the rheumatic infection was mild and prolonged. Hall and Ichioka[1] made a minute histo-pathologic study of cases of calcific aortic stenosis both with and without other valvular disease, and found support for the belief that rheumatic fever is the common background of all of them. Similar investigations were made by Karsner and Koletsky,[12] and resulted in the same conclusion.

Other investigators of this subject have been able to find examples of both rheumatic and sclerotic deformities of the aortic valve in their material (Margolis, Ziellessen and Barnes[13]). The group of cases studied by Sohval and Gross[14] was found by their criteria to include 32 examples of rheumatic endocarditis, of which 19 were multivalvular, and 18 instances of Mönckeberg's aortic valvular sclerosis. In the latter group 3 cases showed some rheumatic stigmata in one or another part of the heart, and 4 showed syphilis of the aorta. These authors concluded that Mönckeberg's sclerosis of the aortic valve is distinguishable from rheumatic disease, and suggested that deformity of the valve by any disease is possibly a predisposing cause of the former process.

One of the arguments advanced against the existence of primary calcific sclerosis of the aortic valve is the observation that arteriosclerosis is usually of slight degree in the adjacent aorta. This, however, may be regarded as a phenomenon resulting from the protective effect of the aortic stenosis on the adjacent aortic wall, shielding it from the force of the blood flow. Such an effect is observed in peripheral arteries, where the wall beyond a calcified plaque is frequently found free of atheromatous degeneration. On the other hand, the aortic wall at a point opposite the valve orifice frequently shows a sclerotic plaque, marking the zone of impact of the narrow stream of blood formed by the stenosis. Hall and Ichioka[1] make reference to this, and call it an "impingement" plaque.

If then the aorta is usually not markedly sclerotic, one may ask how does Mönckeberg's sclerosis of the aortic valve develop, since it is stated to be a process originating in the aorta? This is only an apparent rather than a real objection, since the point of origin is not the aorta in general but that small portion within the sinuses of Valsalva along the insertion margins of the cusps. In this area all of our cases show atheromatous degeneration and calcification. The underlying causes of these changes may be any combination of mechanical, toxic, metabolic and infective phenomena allegedly associated with arteriosclerosis (Leary[15]). The exposed position of the aortic cusps, their

rapid to-and-fro flexion in the blood stream and the fixed position of the aortic ring where the sinuses of Valsalva receive the full impact of the regurgitant force after each systole are basic facts. The additional stress which may result from the presence of congenital bands or cusp deformities, or from inflammatory thickening or adhesions must also be considered. Some authors (Libman,[7] Reich[2]) believe that calcific aortic stenosis sometimes results from the healing of vegetative endocarditis. In the present group of cases, no example of this sequence of events has been recognized.

Summary. The great frequency of gross and histologic lesions of a type generally recognized as rheumatic but occurring in the absence of notable deformity, seems to us to invalidate an assumption that any coincident lesion necessarily has a rheumatic etiology. In this study of 31 cases there has purposely been no attempt to exclude those in which other valvular lesions were present as well as calcific aortic stenosis. The most frequently co-existent lesion was mitral stenosis (55%). Rheumatic aortic valvular disease was found in some cases in which no other cardiac lesion could be detected. Mönckeberg's sclerosis of the aortic valve was found in 2 hearts in which the mitral valves revealed definite evidence of inactive rheumatic inflammation, and in 1 in which syphilitic aortitis was present.

Conclusion. Thirty-one cases of calcific aortic valvular stenosis occurred in a series of 500 consecutive autopsies. Pathologic studies lead us to the belief that 17 were rheumatic in etiology and the rest are examples of Mönckeberg's sclerosis of the aortic valve.

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A TENTATIVE TEST FOR PHEOCHROMOCYTOMA*

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Paroxysmal hypertension and associated symptoms characteristic of the clinical syndrome caused by pheochromocytoma frequently have been described and are well known; but the differentiation from such clinical conditions as coronary occlusion, hyperthyroidism, histamine cephalgia, migraine, menopausal states and anxiety states, patients who are hyper-reactors, and patients who have persistent hypertension may be difficult. The most confusing cases, in our experience are the hyper-reactors and those in which the patients have essential hypertension and whose blood pressure is extremely labile. Patients who have anxiety states also cause difficulty because of their frequent description of attacks or spells of various kinds of symptoms.

In the past the diagnosis of suspected pheochromocytoma was confirmed by the attacks which characterized this clinical entity. These attacks, which might be either spontaneous or induced, were precipitated by various means including physical exertion, change in position such as rising from the recumbent to the upright position, turning on the side of the tumor, massage of the abdomen on the side of the tumor, immersion of the extremities in cold water or administration of insulin or epinephrine. Since none of these methods of inducing attacks is dependable and since the opportunity to observe the patient in a spontaneous attack may not present itself, it is apparent that a simple procedure that would induce attacks at will would be of great help in diagnosis.

Beer, King and Prinzmetal,[1] in 1937, and Hyman and Mencher,[5] in 1943, were able to demonstrate an epinephrine-like pressor substance in the blood of several patients during attacks caused by pheochromocytomas. Since attacks owing to such a tumor are similar to those produced by large injections of epinephrine and since large amounts of epinephrine have been extracted from many of the tumors investigated, it is logical to suggest that the attacks are due to sudden massive discharges of epinephrine from the tumor into the circulation.

Hyman and Mencher[5] also produced attacks of paroxysmal hypertension by the cold pressor test and by the injection of histamine. However, they failed to mention whether they considered the latter a suitable means for voluntary production of an attack.

In 1939, Horton and one of us (G. M. R.)[4] demonstrated an epinephrine-like response in the case of a patient who was hypersensitive to cold subsequent to a histamine-like response to the immersion of one hand in cold water. Also, Best and Taylor,[2] in 1943, reported

* Read before the Central Society for Clinical Research, Chicago, Nov. 3, 1944.

that histamine and epinephrine are antagonistic in their effects on the capillaries and blood pressure.

As a result of these observations, an intravenous infusion of histamine was given to a patient in whom the diagnosis of pheochromocytoma was made in order to determine whether this drug could be used later during operation to counteract the increase of blood pressure which usually occurs during the surgical procedure. Each time the infusion was started, irrespective of the rate of flow, an attack was induced which was identical with the patient's spontaneous attacks. Small amounts of histamine base injected at another time produced similar attacks. Since it seemed possible that this procedure might be used as a test for pheochromocytoma, the present study was begun.

Since the importance of early diagnosis in cases of pheochromocytoma, methods of localizing the tumor, type of surgical procedure, anesthetic agent, and care of the patient before and after operation have been stressed on numerous occasions, no attempt will be made to elaborate on these subjects. Our purpose is to present a simple clinical test which we believe will precipitate an attack of paroxysmal hypertension in a patient who has pheochromocytoma. A preliminary report on the test has been published previously.[7]

Method of Study. *Selection of Subjects.* Fifty-one persons were divided into four groups, as follows: Group 1, 9 normal persons whose ages ranged from 20 to 48 years. Group 2, 22 hyper-reactors to the cold pressor test, whose ages ranged from 19 to 59 years. The basal blood pressure of the patients in Group 2 was less than 140 mm. of mercury systolic and 90 mm. diastolic; the rise of blood pressure during the cold pressor test was more than 22 mm. of mercury systolic and 15 mm. diastolic. Group 3, 16 patients who had well-established hypertension whose ages ranged from 32 to 62 years. The basal blood pressure was more than 140 mm. of mercury systolic and 90 mm. diastolic. Group 4, 4 patients who were suspected of having a pheochromocytoma with ages ranging from 39 to 59 years.

Procedure. The test as employed consisted of placing the person in a recumbent position for 30 minutes or until the blood pressure and pulse rate had attained or approximated the basal level. Before injection, in order that psychic stimuli could be ruled out, the patient was told the sequence of events to expect from the injection. With the blood pressure cuff on one arm, 0.05 of histamine base in 0.5 cc. of normal saline solution or 0.025 mg. in 0.25 cc. of normal saline solution was injected intravenously into the opposite arm. Readings of blood pressure and pulse rate were made at intervals of 1 minute for from 10 to 15 minutes. Both subjective and objective symptoms were noted. In addition, a cold pressor test was done on each person.

Results. *Group 1.* After injection of histamine, most of the 9 normal persons had only slight flushing of the face and mild headache which frequently disappeared at the end of 5 minutes. The blood pressure first decreased and then increased from the basal level to the approximate elevation obtained during the cold pressor test. The basal blood pressure ranged from 95 to 130 mm. of mercury systolic and from 65 to 74 mm. diastolic. The systolic blood pressure during the cold pressor test ranged from 112 to 150 mm.; during the histamine test it ranged from 110 to 150 mm. The diastolic blood pressure during the cold pressor test ranged from 70 to 85 mm. of mercury; during the histamine test it ranged from 64 to 74 mm. The

average rise of blood pressure during the cold pressor test was greater than that during the histamine test (Table 1). The results of the histamine test were regarded as negative. Figure 1, *left*, shows the response of a normal person to the intravenous injection of histamine and to the cold pressor test.

TABLE 1.—AVERAGE ELEVATION OF BLOOD PRESSURE AFTER THE COLD PRESSOR TEST AND AFTER THE INTRAVENOUS INJECTION OF 0.05 MG. OF HISTAMINE BASE

		Average blood pressure, mm. of mercury				
Cases	Classification of patients	Basal	During cold pressor test	During histamine test	Increase during cold pressor test	Increase during histamine test
9	Group 1: normal	109/70	127/87	124/77	18/17	15/7
22	Group 2: hyper-reactive	120/78	157/104	149/88	37/26	29/10
16	Group 3: hypertensive	162/104	202/125	198/118	40/21	36/14

Group 2. Twenty-two patients who were hyper-reactors to the cold pressor test had flushing of the face and headache after injection of histamine. These reactions were similar to those of the normal persons in Group 1. In 1 instance, histamine cephalgia developed as a result of the injection of histamine. The basal systolic blood pressure ranged from 100 to 130 mm.; the basal diastolic pressure ranged from 60 to 95 mm. During the cold pressor test the systolic blood pressure ranged from 132 mm. of mercury to 202 mm. and the diastolic ranged from 88 to 114 mm.; during the histamine test the systolic blood pressure ranged from 118 to 180 mm. and the diastolic blood pressure ranged from 64 to 120 mm. As in Group 1, the average rise of blood pressure during the cold pressure test was greater than that during the histamine test (Table 1). The results of the histamine test were considered to be negative. Figure 1, *right*, shows the response of one patient in Group 2 to the intravenous injection of histamine and to the cold pressor test.

Group 3. Sixteen patients who had well-established hypertension had more severe headaches after injection of histamine than were experienced in the previous group. These headaches rarely disappeared before 10 minutes and in some instances lasted 15 minutes. Circumoral pallor occurred in 6 cases. The average increase from the basal pulse rate of 78 beats per minute was 39 beats per minute. The average rise of blood pressure from the basal level was greater during the cold pressor test than during the histamine test (Table 1). Figure 2 shows the response of 1 patient in Group 3 to the intravenous injection of histamine and to the cold pressor test. Since no subjective symptoms other than tachycardia, circumoral pallor in 6 instances and headache occurred after injection of histamine, the results were regarded as negative.

Group 4. In contrast to the cases in the first three groups, in 3 of the 4 cases in which the patients were suspected of having a pheochromocytoma a definite attack was produced by the injection of histamine.

Since the first case already has been reported,[6] only features particularly important to the present discussion are included here. The other 3 cases are described in detail.

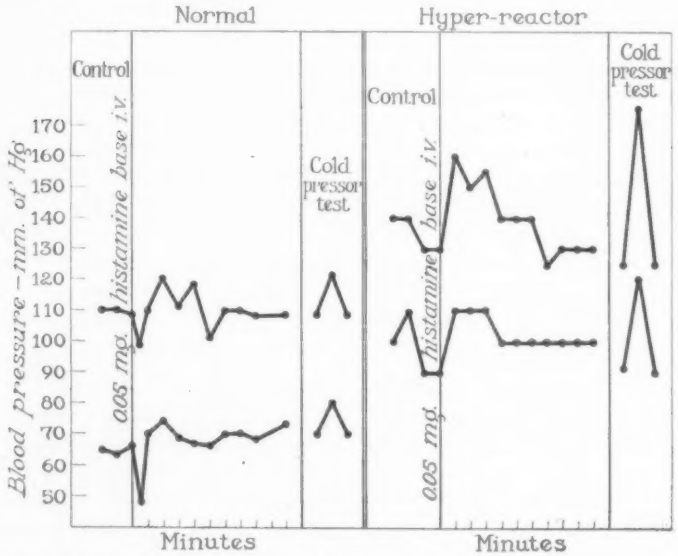

FIG. 1.—*Left*, blood pressure response of a normal person to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test. *Right*, blood pressure response of a hyper-reactor to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test.

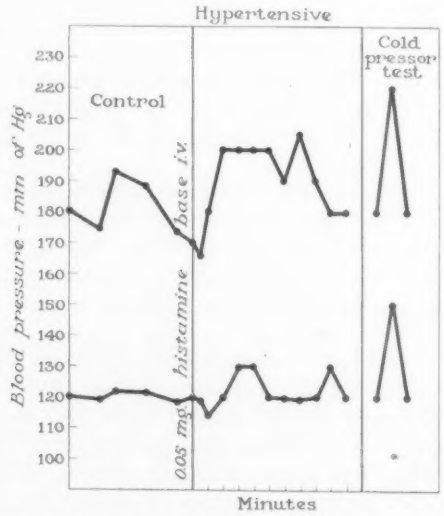

FIG. 2.—Blood pressure response of a patient who had hypertension to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test.

Report of Cases. CASE 1. In this case, that of a woman aged 41 years, attacks could be precipitated by exercise, change of posture and abdominal

massage. They were not precipitated by the cold pressor test, subcutaneous injection of 15 units of insulin, 1 cc. of 1:100,000 dilution of epinephrine or an intravenous infusion of 1 to 2 mg. of acetyl-β-methylcholine chloride (mecholyl chloride) during 15 minutes, but they were precipitated by an intravenous injection of histamine. An attack was induced on one occasion by slow infusion of histamine and on 4 occasions by rapid intravenous injections of either 0.05 mg. or 0.025 mg. of histamine. After surgical removal of the tumor, the same test produced no significant change in blood pressure.

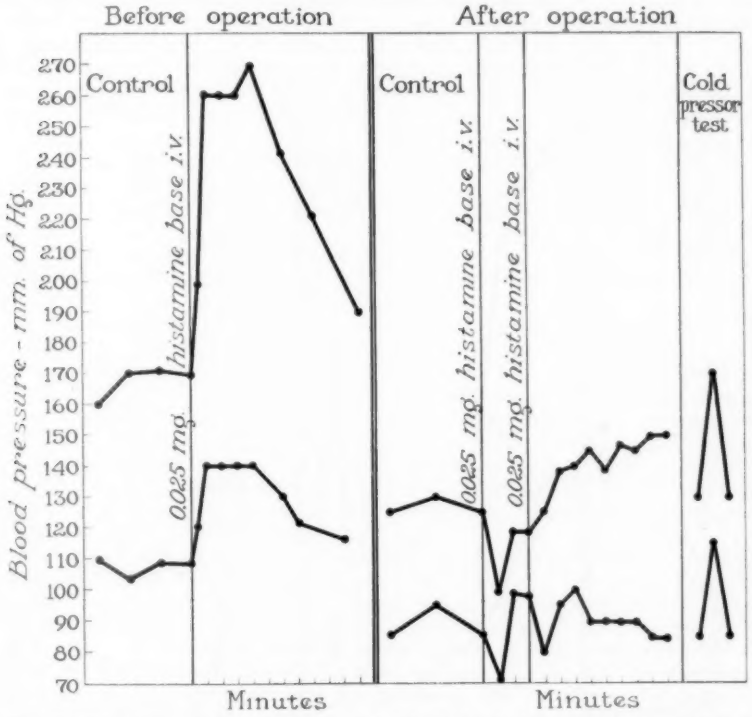

FIG. 3.—Blood pressure response of a patient who had pheochromocytoma (Case 2) to an intravenous injection of 0.025 mg. of histamine base before and after operation and to the cold pressor test.

CASE 2. A man, 59 years of age, was admitted to the Mayo Clinic on Nov. 5, 1943. For the last 3 years he had had attacks from 1 to 10 times a day. The attacks were always sudden in onset and generally lasted from 10 to 15 minutes. They were characterized by a generalized ill feeling, anxiety, fright, marked distress through the abdomen and chest, palpitation, headache which was not particularly severe, numbness of the left hand and arm and blanching of the left second and third fingers and left second and third toes.

The results of physical examination were not significant. The mean blood pressure over a period of 24 hours was 170 mm. of mercury systolic and 110 mm. diastolic. There was narrowing and sclerosis, Grade 2, of the retinal arterioles with a few small retinal hemorrhages. The grading was on the basis of 1 to 4, in which 1 represents the least and 4 the greatest degree. The only positive laboratory finding was evidence of mild renal insufficiency and a stone in the pelvis of the right kidney.

Before the patient came to the Mayo Clinic, the home physician observed him in several attacks which were induced by pressure on the left side of

the abdomen. Apparently the attacks also could be induced by bending the body to the left or by straining at stool. Likewise under our observation, the blood pressure rose from 140/100 to 264/148 on 1 occasion after an attack induced by pressure on the left side. A similar attack occurred, produced by the administration of histamine, in which the blood pressure rose from 170/140 to 260/140 (Fig. 3).

Because these attacks could be induced by pressure on the left side of the abdomen and by the intravenous injection of histamine, we concurred in the diagnosis of left pheochromocytoma which was made by the physician in the patient's home locality.

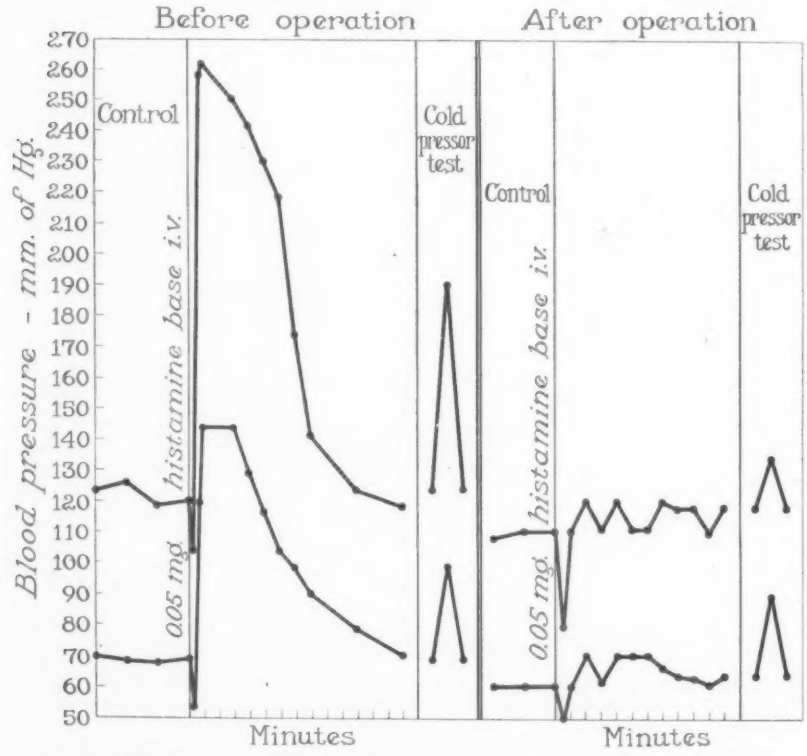

FIG. 4.—Blood pressure response of a patient who had pheochromocytoma (Case 3) to an intravenous injection of 0.05 mg. of histamine base before and after operation and to the cold pressor test.

On Nov. 19, 1943, the left suprarenal region was explored but no tumor was found; the wound was closed, the patient turned over, the right suprarenal region explored, the tumor located immediately and removed easily. The patient's convalescence was uneventful and he was dismissed from the hospital on the 15th postoperative day. The result of repetition of the histamine test on the 16th postoperative day was negative.

CASE 3. A man, 59 years of age, was admitted to the clinic on July 3, 1944, complaining of headaches of only 6 weeks' duration. These headaches usually occurred after the act of voiding. They were severe, sudden in onset, and were associated with considerable epigastric pain extending through to the back and up to the chest. In addition, there was palpitation and blurring of vision, sometimes to complete blindness. These attacks occurred from 1 to

4 times a day and lasted from 4 to 5 minutes. The patient had noticed some dull intermittent pain in the right loin, but this was not related to the urinary tract and was not associated with the attacks. He had had diabetes mellitus for 15 years.

The results of *physical examination* were essentially negative. The blood pressure was 110 mm. of mercury systolic and 80 mm. diastolic.

Ophthalmoscopic examination showed narrowing and sclerosis of the retinal arterioles, Grade 1. The results of laboratory studies were negative except for a fasting blood sugar of 274 mg. per 100 cc. of blood.

During the time the patient was studied in the hospital, he was observed in one attack after he had voided. No blood pressure readings had been obtained just prior to the attack but the readings always had been within normal limits. One minute after the attack started the blood pressure rose to 250/170; in 2 minutes it was 270/122 and in 10 minutes it had dropped to 135/80.

Two attacks were induced by the intravenous injection of 0.05 mg. and 0.025 mg. of histamine, respectively. The patient informed us that these attacks were identical to his spontaneous attacks and complained of a pounding, excruciating headache and severe epigastric pain extending to the back and chest. He was frightened and refused to lie quietly on the bed. In the first attack, the blood pressure rose from a basal level of 118/60 to 260/142. The attack subsided in 10 minutes, at which time the blood pressure was again normal (Fig. 4).

The diagnosis was pheochromocytoma. Because these tumors occur most frequently on the right side of the body,[3] and because the patient had had vague pains through the right flank, it was decided to explore this side first. Accordingly, on July 18, the right suprarenal region was explored, but no tumor was found. The incision was closed, the patient turned over and the left side explored, and the tumor found at the upper pole of the left kidney and successfully removed. The first 3 postoperative days were stormy, but thereafter convalescence was without incident. The result of the histamine test on the 17th postoperative day was negative. The patient was dismissed on the 19th postoperative day.

CASE 4. A dentist, 39 years of age, was admitted to the clinic on June 21, 1944, complaining of attacks of tachycardia and flushing of the face of 3 months' duration. These attacks, of which he had had 4, lasted about ½ hour. There was no associated pain but the attacks were annoying to the patient.

The results of *physical* and *laboratory examinations* were negative except for a mass in the left upper quadrant of the abdomen. This mass was considered to be the spleen. The diagnosis was indeterminate but the probability of a pheochromocytoma was considered. An attempt was made to induce an attack by injection of histamine but the reaction was unlike the symtoms of which he complained and the histamine test was negative. The patient was informed that the possibility of his having a pheochromocytoma was remote, but because of the mass in the left upper quadrant of the abdomen, he chose to undergo an abdominal exploration.

On July 27, exploration was undertaken through a primary upper right rectus incision. The spleen was slightly enlarged, but the results of exploration of the liver, gall bladder, stomach, duodenum and both suprarenal regions were entirely negative. After operation the histamine test was again negative.

Comment. The histamine test was performed in 9 cases in which the persons were normal (Group 1) and in 42 cases (Groups 2, 3 and 4) in which differentiation of paroxysmal hypertension owing to a pheochromocytoma from various other clinical conditions was thought necessary. The results of the test were regarded as negative in 39 of the 42 cases. In 4 of these 39 cases in which an opportunity was presented for exploration of the suprarenal regions, no tumor was found.

Since May 1, 1943, we had the opportunity of observing 3 cases in

which a correct clinical diagnosis of pheochromocytoma was made. The rapid injection of small amounts of histamine produced attacks identical with the spontaneous attacks of which these patients complained, thus affording us the opportunity of observing them in attacks. An attack was induced 5 times in 1 case and twice in another; the other patient refused to allow us to induce more than 1 attack. In each attack the systolic and diastolic blood pressure rose markedly and then promptly returned to basal levels within 10 minutes, when the attack subsided.

In each of the 3 cases in which the results of the histamine test for pheochromocytoma were positive, the tumor was removed successfully and the patient was restored to normal health. The tumors yielded from 50 to 682 mg. of crystalline epinephrine. During the postoperative period of these patients, repetition of the histamine test gave negative results.

Summary. An intravenous injection of 0.025 mg. or 0.05 mg. of histamine base was given to 51 persons who were divided into four groups as follows: Group 1, normal persons whose ages ranged from 20 to 48 years; Group 2, hyper-reactors to the cold pressor test whose ages ranged from 19 to 59 years; Group 3, patients who had well-established hypertension whose ages ranged from 32 to 62 years; and Group 4, patients suspected of having pheochromocytoma, whose ages ranged from 39 to 59 years.

In the first three groups the blood pressure rose to a level somewhat less than the elevation obtained by the cold pressor test. Except for flushing of the face with subsequent headache, which was most intense in the patients with severest hypertension and pronounced tachycardia, no other symptoms were present. The results of the test were regarded as negative. In 1 instance, typical histamine cephalalgia was produced by this amount of histamine base.

When histamine base was given to 3 patients who had pheochromocytoma, the blood pressure rose approximately 100 mm. more than the elevation obtained by the cold pressor test. This elevation of blood pressure was accompanied by the characteristic symptoms of a typical spontaneous attack.

Although the number of cases in this series is small, the intravenous injection of small quantities of histamine base may be considered tentatively as a worth-while test in distinguishing the syndrome of pheochromocytoma from other clinical conditions.

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A STUDY ON THE PREVENTION OF MUMPS ORCHITIS BY GAMMA GLOBULIN*

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Although the involvement of the salivary glands in mumps is seldom incapacitating, the orchitis which frequently complicates the disease in adults gives rise to considerable pain and discomfort, results in lengthy hospitalization, and causes much mental disturbance over the fear of subsequent sterility. For these reasons it appeared important to investigate the possibility of reducing the incidence of orchitis complicating outbreaks of mumps in the armed forces.

In the spring of 1944 an outbreak of the disease at Fort Benning, Georgia, presented the opportunity of determining the value of gamma globulin in the prevention of orchitis.

Series 1. Gamma globulin prepared from mumps convalescent serum was used in the initial series. The serum, collected from 395 patients at an army camp 1 to 3 months following recovery from mumps, was processed in the Department of Physical Chemistry of the Harvard Medical School through the courtesy of Dr. E. J. Cohn and Dr. J. L. Oncley:† 20 ml. of globulin were given intramuscularly to alternate patients admitted to the Station Hospital at Fort Benning with parotitis. Only those patients whose glandular swelling had been present 24 hours or less were admitted to the study. Patients who complained of testicular ache at the time of admission to the hospital were excluded. Physical examinations were performed daily on all patients and careful records were maintained. The patients were hospitalized for approximately 1 month in order to insure personal observation of any cases of orchitis which developed. In the event that globulin delayed but did not prevent the occurrence of orchitis a further check on the injected men was made 1 month after discharge from the hospital. The injected men and controls were confined to bed from the time of admission to the end of the 1st week of hospitalization but thereafter they were permitted to walk about the ward.

The results of this study are recorded in Table 1:

Table 1

		No. patients who developed orchitis	Incidence of orchitis (%)
No. of injected patients . .	51	4	7.8
No. of controls	51	14	27.4

* This work was carried out under the direction of the Commission on Measles and Mumps of the Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, 1818 H Street, N.W., Washington, 25, D. C.

† The preparation and testing of the globulin was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

Of the total patients with mumps studied (502), aside from those concerned with the investigation of the globulin, 25% developed orchitis subsequent to admission. Inclusion of patients with orchitis on admission raised the incidence of this complication to 32%.

Series 2. Because of the small supply of convalescent serum gamma globulin available, the above study was terminated and a similar experiment was conducted using gamma globulin from pools of normal human plasma. Enders[1] has shown that the complement fixing antibody for mumps antigen is concentrated approximately 20 times in this preparation of globulin. Since the titer of antibody is lower than that of gamma globulin obtained from convalescent serum a larger dose was administered to the men in this series. As in Series 1, alternate patients in the first 24 hours of the disease were given globulin. 50 ml. of globulin were administered, half being injected into each buttock. The results of this study are recorded in Table 2:

TABLE 2

		No. patients who developed orchitis	Incidence of orchitis (%)
No. of injected patients . .	67	14	20.9
No. of controls	67	18	26.8

Although these studies involve relatively small groups they suggest that convalescent serum gamma globulin is highly effective in the prevention of mumps orchitis, whereas gamma globulin from normal human plasma is of little value in this respect, nor in the latter group would there appear to be any attenuating effect.

Discussion. Hess[2] in 1915 was the first to employ human antibody, in the form of convalescent whole blood, in the prevention of mumps. Since then several studies have been conducted with mumps convalescent serum in the attempt to prevent the disease, modify its course, or lower the incidence of orchitis. The results of these studies are conflicting. It appears to be the present consensus of opinion that mumps convalescent serum will confer a temporary, brief, passive immunity which is of value in controlling outbreaks of the disease. However, the efficacy of convalescent serum in modifying the course of the disease or in prevention of orchitis is questionable. According to Gordon and Heeren,[3] "the administration of convalescent serum to patients with clinical parotitis in an effort to prevent other manifestations of the disease lacks proof of any worthwhile value." Iversen's series[4] showed a 20% incidence of orchitis in serum treated individuals as compared to 24% in those untreated. De Lavergne and Florentin[5] reported a reduction in orchitis from 24% in their control patients to 4% in their treated ones. In the series reported by Bailey and Haerem[6] 19.9% of the controls developed orchitis and 15.3% of the treated patients developed this complication. The amount of convalescent serum administered in the above studies ranged from 10 to 30 ml. per patient.

Variation in antibody titer of convalescent serum and differences in the dosage administered may account for conflicting results with con-

valescent serum. Bailey and Haerem found that the incidence of orchitis in men receiving serum from convalescent mumps orchitis patients was much lower than in those receiving serum drawn from patients whose disease had been uncomplicated by orchitis. They felt that this difference might be due to the higher antibody titer in the serum of men recovering from mumps orchitis.

The present series differ from those previously reported in the large quantity of serum administered. Since the gamma globulin preparation represents approximately a 20- or 25-fold concentration of human plasma, the initial series which was given 20 ml. of convalescent serum globulin received the equivalent of 400 ml. of convalescent serum or the equivalent (in antibody content) of 4000 ml. of normal pooled plasma. The second series, to which 50 ml. of globulin from normal human plasma were given, received the equivalent of 1250 ml. of normal plasma.

The mumps antibody in these preparations has been estimated by complement fixation tests carried out in Dr. J. F. Enders' laboratory, in the Department of Bacteriology, Harvard Medical School. The mumps antibody concentration, as estimated by the complement fixation test, has been referred to that in a standard preparation of gamma globulin from normal plasma, IIG66. The following table (Enders) gives the approximate results obtained for plasma and gamma globulin solutions from both normal and mumps convalescent donors:

TABLE 3 (ENDERS)

Source of donors	Ratio of mumps antibody (complement fixation test) to standard preparation IIG66	
	Plasma	Gamma-globulin
Normal (American Red Cross blood donors)	0 04	1 0
Mumps convalescent	0 5	10 0

Despite the large dose administered in the present studies it is evident that gamma globulin from pools of normal plasma in the doses employed is of no value in the prevention of mumps orchitis. However, the convalescent serum gamma globulin appears from the present small series to be highly effective and warrants further investigation.

Summary. 1. Alternate patients with mumps parotitis of 24 hours duration or less were given an intramuscular injection of 20 ml. of gamma globulin derived from mumps convalescent serum. The incidence of orchitis in the injected group was 7.8%, in the controls, 27.4%.

2. Alternate patients with mumps parotitis of 24 hours duration or less were given an intramuscular injection of 50 ml. of gamma globulin derived from pools of normal human plasma. 20.9% of the treated patients and 26.8% of the controls developed orchitis.

3. Gamma globulin derived from pools of normal human plasma is ineffective in the dosage employed in the present study in reducing the incidence of orchitis complicating mumps, whereas gamma globulin from mumps convalescent serum appears highly effective in this respect and warrants further investigation.

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THE PHARMACOLOGY AND THERAPEUTIC APPLICATIONS OF ANTI-THYROID COMPOUNDS

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The fact that certain substances possess anti-thyroid activity was brought to the attention of experimentalists in 1928 when Chesney, Clawson, and Webster reported that the prolonged feeding of cabbage to rabbits resulted in hyperplasia of the thyroid gland.[21] They tested practically all of the Brassicæ and found that these plants also effected an enlargement of the thyroid in their animals. Because these materials were known to contain nitrile derivatives, Marine and co-workers[67] tested the cyanides for possible goitrogenic activity; they chose the least toxic of the cyanides, acetonitrile, for their study. A striking thyroid hyperplasia resulted when this compound was injected into rabbits daily for 21 days. Certain aromatic nitriles shared this property but to a lesser degree. Since the cyanides were known to interfere with oxygen utilization, it was concluded that substances which depress oxygen consumption probably increase thyroid activity. Marine had previously postulated that when an increased demand is made upon the thyroid, goitre will result if the iodine supply is deficient. Accordingly, these authors demonstrated that the goitre resulting from the administration of acetonitrile could be prevented completely by iodine. As will be seen later, this fact serves as an important point of difference between the mode of action of the cyanides on the one hand and of the thioureas and related compounds on the other.

Following Marine's work on the chemical production of goitre, there were relatively few investigations until 1941 when a new impetus was supplied by the report of the MacKenzies and McCollum that rats fed sulfaguanidine for a period of weeks developed a marked thyroid hyperplasia.[66] Independently, Richter and Clisby made a similar observation

while studying the chronic toxicity of phenylthiourea in rats.[85,86] Meanwhile, Kennedy, who had been working on the goitrogenic property of Brassica seed, suggested that the active principle of this material might be a thiourea derivative. He therefore tested allyl thiourea and noted that its prolonged oral administration to rats resulted in extreme hypertrophy of the thyroid gland; in preliminary experiments with thiourea he obtained similar effects.[54] These observations[54,66,85,86] were then confirmed and extended by Astwood and co-workers.[7] The conclusion was reached that these substances act by interfering with the synthesis of thyroid hormone.

As a result of these investigations, Astwood instituted a study of the relative effectiveness of 106 compounds derived from thiourea or aniline as inhibitors of thyroid function in rats. He reported that certain derivatives of aniline, particularly the sulfonamides, were active in this regard. In the thiourea group certain derivatives were found more effective than thiourea itself; in decreasing order of activity these were: 2-thiouracil, 2-thiobarbituric acid, s-diethyl thiourea, and 5-benzal-2-thiohydantoin.[1]

Astwood was the first to apply these results to the treatment of human thyrotoxicosis.[2] The dramatic findings reported by him stimulated a large number of studies in animals and man to elucidate the mechanisms and to explore the therapeutic potentialities of these compounds.

Effect on the Thyroid Mechanism. Following the initial reports of thyroid hypertrophy in rats after the prolonged feeding of sulfonamides, phenylthiourea, and thioureas, the MacKenzies and Astwood described in detail the effects of these substances on the thyroid mechanism.[7,63] In the intact animal, the characteristics of thyroid hypofunction were manifest; these included a gradual reduction in the basal oxygen consumption, decreased food intake, and impairment of growth and development. This general picture also appeared in animals fed thiouracil.[1] When rats were given thiouracil from birth, retardation in growth and development occurred.[50] Animals fed these drugs manifested an increased tolerance to low oxygen tensions in accord with the lowered metabolism.[43,44,59]

At postmortem examination the thyroid glands were grossly enlarged and hyperemic. Histological examination revealed varying degrees of colloid loss, increased vascularity, and increase in the height of the acinar epithelium. In many follicles papillary projections of the epithelium protruded into the lumen with extensive desquamation of cells. In some instances the acini had disappeared and the extensive growth of follicle epithelium formed a contiguous cellular mass. At a time when the most severe hyperplasia existed, the cellular pattern in all glands studied remained orderly with no suggestion of neoplasia. To the present there have been no reports of malignant changes occurring either in animals or man as a result of the administration of these substances.

The overall picture observed was one of varying grades of hyperplasia of the gland paradoxically associated with indications of hypothyroidism in the intact animal. Upon withdrawal of the drugs, the evidences of hypothyroidism disappeared and the histologic changes regressed toward normal.

Mechanism of Action. The mechanism by which the anti-thyroid substances exert their effects has received considerable attention. The course of events in animals after the administration of these compounds was propounded initially by Astwood *et al.* and the MacKenzies. They concluded that the effects observed were due to an interference with the production of thyroid hormone.[7,63] This was based on the following facts: It was learned that the presence of the pituitary was essential for the production

of thyroid hyperplasia with these drugs. In hypophysectomized rats the administration of these agents had no effect on thyroid histology; regressive changes were noted in the thyroids of these animals just as in untreated hypophysectomized rats. An attempt to restore the normal situation in the hypophysectomized rat by the concurrent feeding of whole pituitary powder and anti-thyroid drug made possible only the maintenance of a normal histologic picture with little evidence of thyroid stimulation. It seems clear from this that these materials do not cause the hyperplasia by a direct action on the thyroid, but rather that it results from pituitary stimulation.

In view of the indications of an augmented pituitary drive, one might expect to demonstrate an increase in the thyrotropic activity of the blood and pituitary of treated rats. Gordon, Goldsmith, and Charipper were unable to show this in rats fed sulfadiazine and thiourea for a prolonged period. Indeed, the thyrotropic activity of the blood serum and pituitary from these animals was less than that of untreated controls. In contrast, thyroidectomized rats, after 6 months, possessed an increased quantity of thyrotropic activity in the blood and pituitary.[41,46] This does not necessarily contradict the concept of an increased thyrotropic activity in the drug treated rats, but rather indicates an increased utilization and resultant inactivation of thyrotropic hormone by an enlarging thyroid gland. Proof that thyrotropic hormone is capable of stimulating the thyroid gland of thiouracilized rats has been shown from a metabolic standpoint. The thyroids of such animals exhibited an increased oxygen utilization *in vitro*. This increased respiration could be augmented further by previous treatment of the animals with both thiouracil and thyrotropic hormone.[53] This is consistent with the anatomical finding of more severe hyperplasia of the thyroid in rats treated with both substances rather than with either alone. These results therefore are in harmony with the hypothesis that in animals treated with these anti-thyroid drugs, there is an increased thyrotropic activity on the part of the pituitary. This is not the result of a direct action on the pituitary, but may be looked upon as a reflex effect.

That the effects of these compounds can be completely circumvented by thyroxin was the next important point in the elucidation of the mechanism of action. It was learned that the feeding of sulfaguanidine to rats did not prevent the calorigenic action or toxic effects of administered thyroid substance. Furthermore, it developed that the goitrogenic property of any of these compounds could be abolished by exogenous thyroxin.[1,7,27,63] The metamorphosis of tadpoles induced by the injection of thyrotropic hormone could be inhibited by thiouracil, while that induced by thyroxin could not.[51] This principle has been utilized as the basis of an assay procedure for thyroid hormone in which the amount of thyroxin necessary to maintain or restore the normal thyroid weight of thiouracilized animals was determined.[27,82] These facts show that the hypothyroid state resulting from the administration of these agents is not produced by an inhibition of the action of thyroid hormone.

It has been seen from earlier work that the hyperplasia of the thyroid following cyanide administration could be prevented completely by the administration of iodine.[67] In contrast to this, the feeding of large supplements of iodine was without effect on the hyperplasia occurring after the administration of sulfonamides, thiourea, and thiouracil.[17,63] The administration of organic iodine in the form of di-iodotyrosine exhibited but slight antagonism toward thiouracil.[27] This substance, a precursor of

thyroxin, was approximately 4000 times less effective than the latter in preventing thyroid hyperplasia. Therefore, the mode of action of these goitrogens, unlike that of the cyanides, is not associated with an iodine deficiency. In this laboratory we observed that the administration of iodide to rats prior to a course of thiouracil retarded the enlargement of the thyroid.[86a] This is explained on the basis of previous storage of hormone as the result of iodine, so that reflex pituitary stimulation is delayed when hormone formation ceases. Applications of this principle have been observed clinically.

On the basis of the results described, it was concluded that these substances interfere with the synthesis of thyroid hormone in the thyroid gland. In response to the gradual loss of available hormone, the anterior pituitary is activated, and the subsequent elaboration of thyrotropin produces an ineffectual hyperplasia of the thyroid. The resultant effect on the intact animal is similar to that seen after surgical ablation.

The details of the mechanism by which the synthesis of thyroid hormone is prevented have not yet been explained fully. Because of the failure of inorganic iodine to circumvent the block in hormone synthesis the conversion *in vitro* of inorganic iodine to organically bound iodine was examined. Franklin and Chaikoff, utilizing surviving thyroid slices demonstrated that sulfanilamide inhibited the conversion of iodine to di-iodotyrosine and thyroxin.[34] Baumann, Metzger, and Marine reported that in animals treated with thiourea there was rapid loss of both thyroxin and non-thyroxin iodine from the thyroid.[11] Further, the administration of iodide and di-iodotyrosine had no effect on this; the excess iodine was excreted promptly in the urine. Thyroid iodine loss also resulted in animals treated with thiouracil in contrast to glands made hyperplastic by thyrotropic hormone.[5,23] These findings were confirmed by tracer studies with radioactive iodine in normal and thiourea fed rats. Analysis of the thyroids from the treated rats disclosed no appreciable concentration of radioactive iodine in any form. The glands from controls contained a considerable amount chiefly in organic combination.[55] The feeding of thiouracil to rats also interfered with the incorporation of injected radioactive iodine into di-iodotyrosine and thyroxin.[37] In these studies it was found when thiouracil was withdrawn from the diet, that the amount of radioactive iodine converted to thyroxin increased with time. Full recovery of the iodine concentrating capacity of the thyroid was evident 14 days after the withdrawal of thiouracil. A comparison of the effects of thiouracil and thiocyanate on the iodine concentrating capacity of the thyroid *in vivo* has been made. The concentration of labeled iodine in the glands of the thiouracil animals was well below that of the controls. However, in the case of the thiocyanate treated rats, the quantity of radioactive iodine in the thyroid was significantly greater than that of the controls.[81] This provides an illustration of the difference in the iodine metabolism of the thyroid as affected by a goitrogen inhibitable by iodine and by one that is not.

Certain quantitative aspects of the action of thiouracil in inhibiting the *in vivo* iodine uptake by the thyroid have been investigated with radioactive iodine. In the chick, this inhibition was found to be at a maximum 1 hour after the injection of thiouracil and to be lost gradually over 24 hours. The degree of inhibition produced by submaximal doses proved to be a linear function of the logarithm of the dose. In contrast to the rapid loss of the iodine concentrating capacity of the thyroid after injec-

tion of thiouracil anatomic changes were not in evidence for at least 5 days.[57]

With the use of radioactive iodine the similarity between the hyperplasia produced by thiouracil and thyrotropic hormone has been supported. It was first demonstrated that the anatomic changes in the chick thyroid occurring after thiouracil were indistinguishable from those seen after thyrotropic hormone. The similarity was further manifest from the functional standpoint in that the glands made hyperplastic by thiouracil acquired, after thiouracil was withdrawn, a capacity to collect radioactive iodine in amounts greater than controls and comparable to that collected by thyroids made hyperplastic with thyrotropic hormone.[56]

The disturbance in the iodine metabolism brought about by these compounds has also been investigated *in vitro;* reference has already been made to the initial step in this direction.[34] In an extension of this work it was learned that sulfonamides which inhibit the conversion *in vitro* of radioactive iodine to di-iodotyrosine and thyroxin had little effect on the iodine concentrating capacity of surviving thyroid slices.[35,88] Further studies have shown that thiourea, allylthiourea, thiouracil, p-aminobenzoic acid, and thiocyanate were all capable of depressing the conversion of radioactive iodine to di-iodotyrosine and thyroxin. With the exception of thiocyanate, these substances at high concentrations did not interfere with the uptake of iodine by the thyroid slices.[36] These results are essentially in accord with the *in vivo* studies on iodine utilization. It must be realized that the failure of the thyroid in the intact animal to concentrate iodine after the administration of these compounds is a result of numerous factors not present in the isolated tissue. The apparent failure of certain iodination reactions to take place probably represents a primary effect of these agents. From these data, the original assumption that these compounds prevent the normal synthesis of thyroid hormone is well supported.

Other possible points of attack on the thyroid mechanism have been explored. Gyorgy, *et al.* have suggested that these sulfhydryl compounds may exert their effects by reason of their ability to retard oxidations.[47] Pertinent to this, it has already been demonstrated that the cytochrome-cytochrome oxidase system is involved in the formation of di-iodotyrosine and thyroxin by the thyroid gland.[26] Dempsey detected the presence of cytochrome oxidase and peroxidase in the thyroid follicle cells by means of the nadi and benzidine reagents respectively. The addition of thiouracil to the reagents easily inhibited the peroxidase, whereas the cytochrome oxidase reaction was not affected. Since it is known that iodide must be oxidized to iodine before it can react with tyrosine, it would seem logical that the inhibition of peroxidase should favor this reaction by allowing for the accumulation of peroxide. The effect of thiouracil on the peroxidase and cytochrome oxidase activity of the thyroid has been confirmed.[52] In addition, it was found not to inhibit the action of xanthine oxidase or of triosephosphate dehydrogenase.[52] The only oxidative enzyme known to be inhibited easily by thiouracil is tyrosinase.[76] These results cast some doubt on the theory that oxidative mechanisms in the thyroid are interfered with by these substances. It is clear, however, that the evidence in this regard is meagre and will require further study.

Absorption, Distribution, and Elimination. Studies have been carried out on the absorption, fate, and elimination of thiourea and thiouracil. Thiouracil has been shown to be rapidly absorbed from the gastro-intestinal tract. This was determined by analysis of segments of the gastro-intestinal tract of rats after the oral administration of thiouracil. It was found that

more than 80% of a single oral dose disappeared from the gastro-intestinal tract within 2 hours. In man the rapidity of absorption was demonstrated by following the concentration of thiouracil in the blood and urine after ingestion. The drug was present in the blood 15 to 30 minutes after doses of 0.1 to 0.2 Gm. by mouth given to a normal fasting man.[101,102] Thiourea has also been shown to be absorbed quickly from the gastro-intestinal tract in man as determined by blood analysis and the rapidity with which it appeared in the urine after ingestion.[16]

Following the ingestion of a single oral dose of thiouracil by a normal fasting individual, the peak concentration in the blood was reached within 15 to 30 minutes. From this point there was a gradual decline in the blood level, with complete disappearance in 48 to 72 hours. The blood concentration could be maintained fairly well by the administration of frequent small doses.[101,102]

On reaching the blood, thiouracil has been found to enter the cellular elements. The concentration in the blood cells was 2 to 7 times greater than in the plasma. A further breakdown revealed that the total thiouracil content of the erythrocytes in a given specimen of blood was roughly twice that of the leukocytes. From a consideration of the relative proportion of red cells to white cells in a given specimen, it was obvious that the individual leukocyte contained much more drug than did the individual erythrocyte. These findings were confirmed by the *in vitro* incubation of blood cells with thiouracil. It was proved that the lymphocytes and granulocytes actively absorb thiouracil from a plasma solution; the red cells were less efficient in this regard.[102]

Thiouracil has been found to be distributed to all body fluids thus far examined. These included cerebrospinal fluid, edema fluid, pericardial fluid, chest fluid, ascitic fluid, urine, and milk. The concentration in the cerebrospinal fluid, edema fluid, and pericardial fluid was approximately that of the plasma. Chest and ascitic fluid contained a concentration equal to that of whole blood. The concentration of the drug in breast milk was about 3 times that of the whole blood.[102]

Thiourea disappeared from the blood even more rapidly than did thiouracil.[16] It appeared in the urine, cerebrospinal fluid, and breast milk. The concentration in the milk approximated that of the serum, whereas there was a delay in its appearance in the spinal fluid.[20] Because of its easy diffusibility, thiourea has been used to measure changes in total body water; the results agree closely with those obtained by metabolic calculation.[25] In experiments on dogs and man, thiourea was found to be distributed throughout a volume of fluid in excess of that ordinarily designated as total body water. These results can most likely be accounted for on the basis of destruction of the drug in the body. In view of this, it has proven unsatisfactory as an agent for measuring body water.[20]

The presence of thiouracil in body tissues was ascertained in man by the analysis of surgical and autopsy specimens. The drug was found in large quantities in the bone marrow, thyroid, ovaries, and pituitary. In general, the concentration in the bone marrow was greater than that in other tissues. It was shown to be present also in the adrenals, pancreas, kidneys, spleen, liver, testes, striated muscle, brain, heart, lungs and prostate. Certain alterations in the condition of the thyroid affect drug storage in the gland. The amount present in adenomatous portions of thyroid tissue was much more than that in relatively normal sections of the same gland.[102] Experiments on guinea pigs have shown that thyrotropic hormone when given in conjunction with thiouracil greatly decreased

the amount of drug stored in the thyroid, whereas the administration of potassium iodide with thiouracil greatly increased drug storage.[105]

Experiments were carried out on rats to investigate the possibility of thiouracil destruction in the body. In view of the rapidity with which it disappeared from the gastro-intestinal tract, attention was first directed to the action of gastric and intestinal contents on the drug. The incubation *in vitro* of thiouracil with the contents from different portions of the gastro-intestinal tract revealed a destruction of the drug by gastric, duodenal, and jejunal contents; material obtained from the ileum was not effective in this regard. That this may be partly accounted for by the action of certain intestinal flora was shown by incubation *in vitro* of thiouracil with bacteria. *Staphylococcus aureus* and beta hemolytic streptococcus destroyed 35 to 50% of the drug, respectively; *E. coli*, however, caused no destruction. Attempts have been made to determine the amount of drug destroyed by the gastro-intestinal tract.

The rate and amount of thiouracil destroyed by body tissue was determined on rats. Results were said to indicate a rapid initial destruction by the body.[101] The capacity of specific rat tissues to destroy thiouracil was tested by the incubation *in vitro* of surviving slices with thiouracil; those tissues studied included kidney, adrenal, pancreas, liver, pituitary, thyroid, and muscle. All were said to destroy the drug.[102] The quantitative data, however, are not conclusive due to certain unexplained inconsistencies.

The nature of the metabolism of thiouracil in the animal organism is as yet uncertain. Examination of the urine of dogs fed the drug has been reported to show positive qualitative tests for uracil and cytosine.[69] This needs to be confirmed. The effect of thiouracil on the excretion of sulfur in man has received attention. It was found that a decrease in ethereal and inorganic sulfur occurred. There was, however, an increased excretion of neutral sulfur. This was partly accounted for by thiouracil itself; the remainder could not be attributed to cysteine, cystine, thiourea, thiocyanate, phenylsulfate, urochrome, or melanin.[101] In rabbits and man, thiourea has been found to produce similar changes in sulfur excretion.[15,101]

Thiouracil is excreted mainly in the urine; none has been found in stools of animal or man. Subsequent to the ingestion of 0.1 to 0.2 Gm. of thiouracil by normal fasting man, a small amount appeared in the urine in 30 minutes. The maximal urinary excretion occurred during the second hour, and excretion progressively declined to minute amounts in 12 to 24 hours. Following an intravenous dose appreciable quantities were present in the urine within 30 minutes. However, the urinary excretion in this instance was said to persist longer than after oral dosage. The amount of thiouracil excreted in the urine varied with the size and frequency of the dose. However, the greater the daily dosage, the lower was the percentage of the total dose excreted.[101,102] Further studies on the distribution, fate, and elimination of thiouracil are necessary.

Thiourea, like thiouracil, has been demonstrated to be excreted chiefly *via* the urine; none appeared in the stool. In man about 75% of an oral dose of thiourea could be recovered from the urine. As previously indicated, this most likely represents a destruction of the drug by the body.[20] The renal clearance of thiourea and certain of its derivatives has been investigated and contrasted with simultaneous urea and creatinine clearances. The filtration and reabsorption of thiourea by the dog kidney approximates closely that of urea.[73]

Methods for the determination of thiouracil and thiourea in body fluids and tissues have been described.[16,19,24,103]

Other Effects of Anti-thyroid Drugs. A number of papers have appeared reporting the effects of these compounds on organs and tissues other than the thyroid. It was stated that in more than 700 microscopic sections made from essentially all of the body tissues from many series of rats, there were no alterations of note with the exception of those occurring in the thyroid gland.[50] Within a reasonable dosage range this is true. Those changes observed in other organs are in general those secondary to hypothyroidism.

The MacKenzies in their report on the effect of sulfonamides and thiourea as inhibitors of thyroid function, described changes in the histological appearance of the anterior pituitary similar to those occurring after thyroidectomy. These consisted of a basophilia with a loss of eosinophiles.[63] This finding has since been confirmed for sulfonamides, p-aminobenzoic acid, thiourea, and thiouracil.[43,60,65] The abnormal histologic picture reverts to normal upon cessation of treatment.[65] The weight of the rat pituitary gland per unit of body weight was not altered by the feeding of either thiourea or thiouracil.[58,104] As previously indicated the changes in the pituitary are a secondary effect.

Investigations have been carried out on the effect of thiouracil and thiourea upon trophic hormones, other than thyrotropin, elaborated by the anterior pituitary. It was found that these drugs did not inhibit either the adrenotropic or gonadotropic hormones. In fact, the activity of adrenotrope was augmented. In addition assay of the pituitary for gonadotrope revealed a greater hormone content in the glands of treated rats.[58,104] It would appear from this that the increased activity of the anterior pituitary following treatment with these drugs may not be limited entirely to the thyrotropic hormone.

The adrenal glands removed from rats treated with sulfonamides, thiourea, and thiouracil have been examined. These glands were reported to be smaller than those from normal animals.[58,60,104] This is in harmony with the findings in thyroidectomized animals. From a functional standpoint the adrenals removed from rats treated with thiouracil manifest a normal oxygen uptake *in vitro*.[53] In 16 human subjects studies were made of the various constituents of the blood and urine which to some extent are known to represent adrenal function. No alterations were discovered to indicate a disturbed function.[98]

In thyroidectomized animals the liver is known to be slightly decreased in size. This however, has not been observed in rats treated with anti-thyroid compounds.[58,60] Liver slices taken from thiouracilized rats possessed a normal metabolic rate.[53]

There has been experimental evidence of kidney changes following anti-thyroid compounds. Atrophic changes with thiourea have been described in rats, similar to those following thyroidectomy,[60] although no significant change in kidney size has been observed.[58] Hematuria with kidney damage occurs after toxic oral doses of thiouracil in normal and thyroidectomized rats.[70] We have also noted hematuria with crystalline deposits of the drug in the kidneys, ureters, and bladder after large doses of thiouracil in rats.[93]

The anti-thyroid agents apparently possess a direct toxic action giving rise to respiratory distress with pulmonary edema. Acutely toxic doses of phenylthiourea, thiourea, and thiouracil produced rapidly fatal pulmonary edema. No other tissues were edematous.[64,70,86]

Experimental evidence showed that thiourea produced changes in the

heart. The heart rate was slowed in rats after prolonged administration. Such animals showed slight atrophy of the heart similar to that seen after thyroidectomy.[60] The heart acquires a tolerance to epinephrine; in these experiments the threshold concentration of epinephrine in the heart muscle necessary to cause cardiac death in rats was determined and was found to be lower for animals pre-treated with thyroxin and higher for animals pre-treated with thiouracil than in the case of the normal.[78]

In accord with the above report, it is of note that thiourea has been shown to inhibit the epinephrine response of certain smooth muscle preparations. This was effected at concentrations that did not interfere with normal behavior of the preparation.[38]

The young of thiouracil treated mothers appeared normal at birth, but had hyperplastic thyroids; developmental retardation was evident by the tenth day. This was thought to result from a placental and mammary transmission of the drug.[50] Other experiments have confirmed and extended this conclusion.[45] Fetuses removed from thiouracil treated females at term contained a drug concentration one-half that of the mother. The amount of thiouracil in the placenta was slightly more than that of the mother.[101]

In view of the clinical experience with these drugs, perhaps the most important side action is that on the bone marrow. Feeding thiourea to rats produced a definite neutrophilic granulopenia which was preventable by the concurrent administration of solubilized liver extract. It was suggested that the active agent of the extract was probably folic acid.[40] A leucopenia and anemia has also been noted in rats fed thiouracil.[104] This effect must undoubtedly be related to the high concentration of thiouracil observed in the bone marrow of all animals treated. In this regard it is noteworthy that in studies on the distribution of radioactive sulfur in the rat, by far the highest concentrations were found in the bone marrow.[89]

Experiments on the effect of thiouracil on the respiration of bone marrow *in vitro* showed that high concentrations of the drug produce a small but significant inhibition. This was more pronounced in marrows made predominantly myeloid. Attempts to reverse this by the addition of pyridoxine or liver extract were unsuccessful.[92]

The serum and homogenized liver of rats treated with thiouracil possessed cholinesterase activities approximately twice those of control animals. The cholinesterase activity of the cerebral hemispheres from these rats was within normal limits.[31]

It was previously pointed out that malignant changes have not been observed in either animals or man treated with these drugs. However, benign and malignant tumors of the thyroid have been produced in rats by the combined administration of allylthiourea and a carcinogen, 2-acetyl aminofluorene. Neither substance alone was capable of inducing thyroid neoplasia.[14] In a recent editorial the question has been raised as to the possibility of clinical cancer occurring during thiouracil treatment of older patients in whom some carcinogenic factor may be present.[30]

Other Anti-thyroid Agents. In 1943 Carter and co-workers described experiments which led to the conclusion that the basal metabolic rate of the rat is controlled by an interaction between thyroxin and an anti-thyroid substance identified as paraxanthine (1,7-dimethylxanthine).[18] The response was such that a daily dose of 20 micrograms orally produced a reduction of approximately 25% in the basal metabolic rate. When this dose was exceeded the metabolic rate rose toward normal and reached this level with double the dose. Above this dosage there was no further response.

Others have been unable to confirm the anti-thyroxin effect of paraxanthine by *in vitro* and *in vivo* experiments.[42,96]

Thiobarbital has been reported to be a more active goitrogen in rats; it was suggested that it is possibly less toxic.[6]

Tetramethyl thiourea has been shown in rats to have properties similar to other thioureas.[95]

Clinical Studies. More than two years have elapsed since Astwood published a report on 6 clinical trials with anti-thyroid drugs.[2] Since then a voluminous clinical literature has accumulated and at the time of this writing reports have been made on more than 1000 cases. Many of these are of short term studies and are merely preliminary, but sufficient long range studies have been carried out to allow some evaluation of the drugs.

Drugs Utilized. In the clinical series thus far published these drugs have been used: thiourea,[49,72,77,91] thiouracil, thiobarbital,[4] 6-ethyl thiouracil,[4] allylthiourea,[48] tetramethyl thiourea,[95] di-ethyl thiourea,[95] and p-aminobenzoic acid.[13] Of these thiouracil has had the most extensive trial.

Dosage. There has been no standard method of dosage accepted and wide ranges of dose have been used in various clinics. All medication was given orally unless otherwise indicated. For the sake of clarity each drug will be considered individually.

Thiouracil. The greatest variations in dosage have been met with in the case of this drug. In early investigations daily dosages of 1 to 1.2 Gm. were not considered excessive,[9,12,49,74,77] and one clinic reports a daily dose of 2 Gm. in one case.[8] It was soon learned that beyond certain limits large doses were no more effective than smaller ones, and a lower scale of doses has been used generally in the last year. Various schedules of initial and maintenance therapy have been employed and of these 2 effective ones deserve special comment. One method[28,84,94,100] has been to give an initial daily dose of 0.6 Gm., to give 0.4 Gm. daily when the basal metabolic rate has fallen halfway to normal, and then to give 0.1 or 0.2 Gm. daily for maintenance as the individual case requires. The second method has been to give 0.6 Gm. daily initially, continuing thus until the basal metabolic rate has fallen within normal limits; then 0.1 or 0.2 Gm. daily are given for maintenance. The doses are divided and given usually as 0.1 Gm. 2, 4 or 6 times daily. Both methods have been equally effective in producing remissions. It would appear from the clinical data that the incidence of toxic reactions may be lower with the use of smaller amounts of the drug. This will be emphasized later.

Thiourea. Thiourea was the first drug used clinically and it was continued until thiouracil became more generally available. Comparatively larger amounts of thiourea were required. The common daily dose was 1 to 3 Gm.[49,77] These amounts were given in divided doses 2 or 3 times daily.

Thiobarbital. Originally thiobarbital was given in doses of 0.2 to 0.4 Gm. daily. This amount has since been reduced to 0.1 Gm. given in 1 or 2 doses.[4]

6-ethyl Thiouracil. The dose for this drug has not been effectively determined and amounts ranging from 0.02 to 0.1 Gm. daily have been tried in the 12 cases reported.[4]

Allylthiourea. This drug has had its only adequate trial in New Zealand. The dose given was 0.4 Gm. daily.[48]

Tetramethylthiourea. This compound has been given initially in doses of 0.6 Gm. daily; this was administered in 3 divided doses. The usual maintenance dose was 0.1 or 0.2 Gm. daily.[95]

Diethyl Thiourea. This substance was given similarly to tetramethylthiourea. Treatment was discontinued in all cases before maintenance therapy could be instituted.[95]

p-aminobenzoic Acid. This aniline derivative was given intramuscularly in daily doses of 1 to 1.5 Gm. for periods ranging from 3 to 9 months.[13]

Astwood reported that the effect of these compounds on the size of the thyroid in rats is a satisfactory guide to their potency in hyperthyroidism in man. Taking thiouracil as the standard with an assigned value of 1, the rat test gives thiourea a value of 0.13, and thiobarbital a value of 1.7. The observations in man show substantially similar relative values for these compounds.[4]

Factors Influencing Therapeutic Response. Nearly all patients with Graves' disease show partial or complete response to thiouracil. The incidence of failure is less than 2%, based on the failure to show significant response after the dosage in current use. It is noteworthy that even in these cases, one-half of the failures were reported in preliminary communications and in some in which the dose or period of trial was manifestly inadequate.

Patients who "escape" from iodine have responded readily to thiouracil.[77,84]

There is great individual variation in the period which elapses between the beginning of treatment and the clinical response. Reports have placed this latent period at from 1 week to 5 months. Pre-treatment with iodine may delay the response to thiouracil. This effect appears to be due to the storage of thyroxin resulting from iodine treatment, and in accordance with the supposed mechanism of thiouracil action, the more thyroxin available at the time, the greater the delay of thiouracil effects.

Patients with toxic nodular goitre also show a delay in the onset of thiouracil response and in these it is also presumed to be due to the higher concentration of thyroxin present in the goitre.[3,4,8,71]

Duration of Therapeutic Response. The ultimate outlook for the patient with Graves' disease under thiouracil therapy cannot be ascertained since the drug has been in use for a period of only 2 years. The indications are that in order to maintain the therapeutic remission it is necessary to continue the drug for a long time. In the more than 1000 cases already reported, approximately 10% continued satisfactorily after the drug was withdrawn. It is noteworthy that in one series of 48 patients in which a thyroid remission was induced by thiouracil therapy for 6 months or longer, the therapeutic effects continued in 77% of the cases when the drug was withdrawn.[8] There seems to be a relationship between the duration of therapy and the tendency to maintain a thyroid remission after the therapy is discontinued. Astwood has advised at least 6 months of treatment.[4] This is of necessity an empirical figure but there does not seem to be any method by which the optimum time can be determined; experience has proved that the promptness of response, the tendency to therapeutic myxedema, the severity of the thyrotoxicosis, the decrease in gland size, and the disappearance of a bruit are not reliable indications for cessation of therapy.[3,8,71] Relapses have been prompt and frequent in patients treated for periods shorter than 6 months. It is important, however, that all patients who relapse can be re-treated successfully with the drug.

A report of 6 cases of thyrotoxicosis treated with p-aminobenzoic acid has been published. The drug was given intramuscularly in large doses

for 3 to 9 months and produced a remission in each patient. These remissions were sustained 4 to 15 months after therapy was discontinued.[13] This work needs confirmation.

Thyrotoxicosis With Complications. Almost every clinical report has contained at least 1 thyrocardiac and experience has shown that cardiac complications are not a contraindication to thiouracil. Indeed there have been recorded 13 instances of auricular fibrillation and 1 instance of paroxysmal auricular flutter reverting to normal rhythm under thiouracil alone.[3,8,12,28,49,68,84]

The other most common complication was diabetes and 2 of the few failures reported have occurred in diabetic patients;[8,84] on the other hand 6 diabetics have been treated successfully for their thyrotoxicosis. Glycosuria disappeared in 2 other patients under treatment with thiouracil.[28]

Four acromegalics have been treated but the reports on them were contradictory.[3,9]

Of exceeding interest were 2 patients who were treated during pregnancy with thiouracil.[29] One was given the drug all during pregnancy until the last month when iodine was substituted; both mother and child were in excellent condition 5 months postpartum. The other was given thiouracil throughout the entire pregnancy; at delivery the child's thyroid was palpably enlarged but receded rapidly. There was no retardation of its growth or development. No mention of breast feeding was made; this would be of import since thiouracil is present in human milk.

There have been 3 other instances reported of thiouracil administered to pregnant women.[68,87,98] In each case the pregnancy and delivery were uncomplicated. No comments were made of any deleterious effects on the child. Apparently the drug may be given with safety in pregnancy.

Effect on the Thyroid in Man. The reactions of the thyroid to thiouracil as described in animals have, in the main, been confirmed in man. Although in animals when the gland changes size during thiouracil treatment there is always an enlargement, in humans the size of the gland may remain unchanged or it may increase or decrease. There are instances in which relatively large doses early in the course of the treatment caused increase in the size of the gland with symptoms of pressure and pain.[4,49,83] In other cases the gland decreased in size, especially after prolonged treatment.[94,99] In cases in which thiouracil produced no conspicuous changes in the gland, the administration of iodine reduced the size of the gland in much the same way as it does in cases without thiouracil.[3] In general it appears that changes in the size of the gland under thiouracil treatment are minimal, and frequently fall within the limits of error in measurement.

The histologic picture in man resembles that found in laboratory animals. Glands removed at operation subsequent to thiouracil therapy showed hyperplasia and increased vascularity. In 2 of 5 cases a statistically significant increase in the mean height of the acinar epithelium occurred after treatment. In the same series mention is made that involution and not hyperplasia was found in glands from patients treated with iodine previous to thiouracil therapy.[80]

Gland activity has been studied by means of blood hormonal iodine levels and by tracing radioactive iodine. It has been shown that the treated gland takes up much less iodine than does the normal, as is the case in the laboratory animal. Under treatment the level of circulating hormonal iodine falls toward normal.[4,61,80,97,99]

Effect on Metabolism. One of the most frequent laboratory procedures in clinical studies on thyrotoxicosis has been the determination of the basal metabolic rate. Study of the literature brings to light certain generalities

which can be made concerning the effect of these drugs on metabolic rate. Early papers showed that the fall in the basal metabolic rate following thiouracil treatment was directly comparable to that seen in the older series treated with iodine.[3,80] The fall appeared to be most precipitous in the first 2 weeks and then gradually became less rapid.[3,94] Unlike the results with iodine there was no tendency "to escape" during continued treatment. In general the higher the metabolic rate, the sharper the decline, although the precise reaction is not predictable. The rate at which the basal metabolic rate fell to normal was variable; in one series the range was from 4 to 108 days but 80% of the patients reached normal in 10 to 40 days.[8] The basal metabolic rate resisted a fall below normal levels.[49]

Other metabolic functions have been studied. It has been stated that the first detectable effect of thiouracil is a fall in the circulating hormonal iodine.[61] Creatinuria was decreased during therapy; this was one of the earliest changes. The creatine tolerance was increased toward normal. In general the circulation time was increased. The earliest study on the metabolic effects of thiouracil was made by Sloan and Shorr.[90] This disclosed that the nitrogen, calcium, and phosphorus balances tended to become progressively more positive. The serum cholesterol level rose; it was noted that it often attained myxedematous levels before the basal metabolic rate gave evidence of myxedema. This was considered a reliable indication for decreasing the dose of the drug.[8]

Effect on Symptoms. It is difficult to tabulate chronologically the order of the disappearance of symptoms after beginning thiouracil therapy. There was agreement that the skin flush, tension, and irritability were the first to disappear and that the tachycardia was the last. The patient usually experienced subjective relief in advance of laboratory evidence of a response to the drug.[3,8,28,49]

Effect on Exophthalmos. For the most part thiouracil and other antithyroid drugs have no effect on the exophthalmos associated with thyrotoxicosis.[4,28,49,90] Apparent decrease in exophthalmos is brought about by a lessened lid spasm and by a gain in body weight during treatment.[3,4,8,9,49] Several cases of an increase in exophthalmos were reported by Barr and Shorr.[8] Combined therapy with thyroid extract or thyroxin has been said to cause improvement in some cases; in none of these latter cases was the action of thiouracil impeded.[22,74,99]

Effect of Added Iodine. We have already mentioned that pre-treatment with iodine may cause a delay in the response to thiouracil. Once thiouracil has acted, however, additional iodine elicits further response. Despite its inability to lead to the formation of thyroxin in a gland under the influence of thiouracil, it appears to reduce the vascularity and to cause persistent bruits to disappear; likewise it is capable of inducing histological involution of the gland.[4,8,80] These effects have prompted the use of iodine late in the thiouracil preparation of the patient for thyroidectomy.[10]

Pre-operative Use. Thyroidectomy has been carried out subsequent to thiouracil therapy in 2 types of cases. These were either patients who developed untoward reactions to the drug or patients in whom the drug was used to test its efficacy in pre-operative preparation. As a pre-operative measure thiouracil is advantageous because it can be used in cases which have become unresponsive to iodine.[75] Probably its most distinct advantage was that the metabolic state more closely approached the normal than with iodine; the patient became a better operative risk. Further, the problem of anesthesia and sedation was more satisfactorily managed.[10] The pre-operative treatment should be carried out until the basal metabolic rate has reached normal levels.

The disadvantages encountered in operation were: increased vascularity of the gland, occasional difficulty in controlling hemorrhage, and occasional difficulty in establishing cleavage planes, the latter particularly in patients who had had previous thyroidectomies.[9,22,71,75] The vascularity and bleeding were controlled to some extent by the addition of iodine in the latter days of thiouracil treatment.[10] The post-operative course of patients pre-treated with thiouracil has been uneventful; no instance of thyroid storm has occurred and only a few post-operative fevers have been reported.[22,71,74,77,99] On the whole, the smoother post-operative course makes thiouracil a distinct improvement over iodine.

Toxic Reactions. The major disadvantage in the use of anti-thyroid drugs has been the incidence of toxic reactions. For the most part these reactions are not serious and all save one are alleviated by withdrawal of the drug or reduction of the dose; the sole exception is agranulocytosis. At present there are reports of 5 deaths directly attributable to these drugs.

The toxic reactions to thiourea most usually encountered were nausea, vomiting, and halitosis. One case of granulopenia and thrombopenia was reported.[72] The reaction occurred 5 weeks after the onset of treatment and after 83 Gm. of the drug had been given. A study of the bone marrow showed a reduction of platelets and mature polymorphonuclear cells. The patient recovered when the drug was discontinued. Fever and maculopapular rash have also been reported.[91]

The toxic reactions to thiobarbital have consisted of fever, arthralgia, and myalgia which occurred in the second week of treatment and which lasted for 4 to 7 days even after the drug was withdrawn. Two other reactions have been described: 1 case of acute liver failure and 1 case of agranulocytosis which terminated fatally.[4]

The toxic reactions encountered thus far with tetramethylthiourea have been fever, rash, and urticaria.[95]

In the case of diethylthiourea all 4 patients treated developed headache, anxiety, palpitation, and slight dyspnea.[95] These are in all probability the result of circulatory disturbances characteristic of this class of compounds.[32]

The reactions to thiouracil have been numerous. Those which occurred with least frequency were: fever,[8] arthralgia, jaundice,[33,68,90] diarrhea,[68] lymphadenopathy,[33,39,68,71] edema of the legs,[12,28,68] urticaria,[68] conjunctivitis,[8,12] low carbon dioxide combining power,[22] oral infections,[71] nausea,[8] crystalluria,[74] and hematuria.[8,74] These reactions were controlled when the drug was withdrawn or the dosage was reduced. Crystalluria was successfully treated in one series by the concurrent administration of sodium bicarbonate.[74] This point needs confirmation for D. R. Gilligan (unpublished data) reports that there is virtually no difference in the solubility of thiouracil in the urine over the physiological range of pH. Not all of these reactions can be traced specifically to the drug; the fever and conjunctivitis could be definitely attributed to the drug since both reactions recurred promptly following a test dose.

The serious reactions to thiouracil have involved the blood and blood-forming organs. Neutropenia has been reported in at least 35 cases; this could be relieved by withdrawal or reduction of the drug. In other cases the neutropenia did not persist even when the drug was continued in the same dose.

The fatal reactions to thiouracil have all been caused by agranulocytosis. At the time of this writing 3 such cases have been reported. These occurred from 6 weeks to 1 year after treatment was begun. Bone marrow studies

have been performed in several cases; all showed a deficiency of the myeloid elements and a maturation arrest in the myeloid series.[62] It is noteworthy in this respect that 1 case of agranulocytosis was foreshadowed by the appearance of immature forms of the myeloid series in the peripheral blood.[49] With improvement the bone marrow precedes the peripheral blood to normalcy. The most important factors in the treatment of agranulocytosis have been the prompt withdrawal of the drug and the control of infection with penicillin.[8] The liver extract advocated on the basis of laboratory experiment has been used in treatment; its value is still uncertain. Pyridoxine hydrochloride intravenously in large doses has been advocated for the treatment of agranulocytosis.[17]

The toxic reactions appeared to be a manifestation of acquired drug sensitization. This was borne out by the fact that subsequent small doses brought about a return of toxic symptoms.

Treatment of Angina Pectoris. A report has been published concerning the effect of thiouracil on angina pectoris.[79] Ten patients were included in the series. The daily dose of the drug varied from 0.4 to 1.2 Gm. Under treatment 8 of the 10 patients were relieved of pain; 4 of them became entirely symptom free. The therapeutic effect was correlated with the fall of the basal metabolic rate to subnormal levels. This report appears to us to be significant in light of the fact that thiouracil increases the tolerance of the rat heart to epinephrine.

In closing, it may be noted that the compounds which have been discussed have proved not only of great value in the treatment of Graves' disease, but have provided a new tool for the investigation of the physiology of the thyroid gland.

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RADIOLOGY

UNDER THE CHARGE OF
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FIBROCYSTIC DISEASE OF THE PANCREAS

BY DAVID G. PUGH, M.D.

IN 1888 Gee described a condition encountered among infants and children which he called "celiac disease." For many years this condition was regarded as a disease entity but gradually it became apparent to various investigators that it was in reality a syndrome which could be produced by more than one disease. This syndrome consists of large pale offensive fatty stools, abdominal distention, anorexia, wasting, stunting of growth and symptoms of deficiency disease.[23] Owing to the type of bulky fatty stools that are usually seen, it is often called "steatorrhea," a term which has become almost synonymous with the term "celiac syndrome." In many cases the symptoms are produced without any clinical or postmortem evidence of pancreatic disease; in such cases the disease is classified as idiopathic steatorrhea or true celiac disease. As the result of many investigations, which are well described by Rauch, Litvak and Steiner,[23] it became obvious that in some cases disease of the pancreas with pancreatic insufficiency was present. These cases have been designated under various terms, such as "pancreatitis, pancreatic disease, atrophy of the pancreas, congenital pancreatic steatorrhea, celiac disease, congenital cystic fibromatosis of the pancreas, agenesis of the exocrin portion of the pancreas, congenital pancreatic disease, cirrhosis of the pancreas and congenital familial steatorrhea" (Wolman).[25] Since the pathologic changes in the pancreas are consistently similar in these cases, it is suitable to designate the condition as "fibrocystic disease of the pancreas" and avoid use of the synonyms.

Most of those who have studied pancreatic insufficiency with steatorrhea due to fibrocystic disease of the pancreas have been impressed by the constant association of chronic respiratory infection. In the past fibrocystic disease of the pancreas has been diagnosed most frequently at necropsy; recently, however, the diagnosis has been made before death in an increasing percentage of cases. If physicians were stimulated to suspect the condition more frequently, the diagnosis could be made with accuracy in many instances. At times this stimulus may be provided by the roentgenologist.

The pathologic picture of fibrocystic disease of the pancreas presented at necropsy is usually typical.[1,9,12,14,23] Few changes can be recognized grossly. There may be infiltration with fat or increased fibrous connective tissue between the lobules. The lobules may be rounded and uneven in size. Occasionally a grating sound may be produced as the knife passes through calcified concretions. The gland may appear firmer than normal and contain tiny opaque grayish yellow nodules. The pancreatic duct is patent in most cases. The histologic appearance may vary considerably, depending on the stage of development of the disease, though certain constant findings are seen in most cases. Dilated ducts and acini contain varying amounts of coagulated secretion. The cells of the epithelial lining

are flattened and, rarely, may be squamous in type. The secreted material occasionally has a laminated appearance and is usually acidophilic. The intra-acinar material stains like mucus and occasionally like fibrin. The acinar parenchyma is atrophied and the interacinar and interlobular connective tissue is increased and may be infiltrated with lymphocytes or mononuclear cells. The islands of Langerhans are usually normal in size and number, although slight but definite abnormality of these has been seen.

In association with the pancreatic changes pulmonary lesions are present almost invariably at the time of death.[1,9,14,23] Grossly these consist of suppurative bronchitis and bronchiectasis with patches of bronchopneumonia and abscesses. The bronchi usually are filled with mucopurulent exudate that is unusually thick and tenacious. Emphysema and atelectasis, usually in combination, are common findings. Thickening of the bronchiolar walls, replacement fibrosis in those portions of the lungs repaired after staphylococcic destruction and diffuse bilateral acute and chronic bronchopneumonia characterize the later stages of the disease. Staphylococcus aureus is present in most cases.

The pathogenesis of fibrocystic disease of the pancreas is not definitely known. Many early investigators regarded it as a congenital deformity which consists of stenosis or atresia of the pancreatic ducts. However, this has been found but rarely. The presence of this condition in the newborn and its early manifestations in infants, to be sure, does suggest congenital origin. A familial tendency has been observed by many who have studied the disease and this is indicated in many of the synonyms that have been used to describe this condition. In this regard, Daniel[7] said, "It must be stated that although the syndrome appears to be familial, often the affected child is the only infant in a large family who has or has had the disease." The congenital nature of the disease also is suggested by the frequency with which other congenital anomalies are found. Harper[12] said the disease was probably congenital. Rauch[23] and his associates thought that the lesions of both the pancreas and the lungs were due to congenital anomalies. They said that there appeared to be a congenital constriction of the pancreatic ducts and of the bronchial passages which might be explained by the embryologic development since the anlagen of the lungs and pancreas develop from a common entodermal tube. Congenital anomaly of the bronchial tree causes it to be more susceptible to infection and in this way they explained the pulmonary infection in this disease.

Patients who have this disease may have vitamin A deficiency. Some observers have suggested that this deficiency may result in obstruction of the pancreatic ducts by masses of desquamated epithelial cells—a concept that is not generally accepted. Parmelee[22] and later Andersen,[1] however, have suggested that the pulmonary infection may be secondary to changes in the bronchial epithelium resulting from vitamin A deficiency. Most observers doubt that vitamin A deficiency is of primary etiologic importance but recognize that it may become a complication.

It is frequently stated that the respiratory infection is probably only the result of lowered resistance. However, in many instances pulmonary involvement is marked before there is much evidence of malnutrition.

Blackfan and Wolbach[6] in 1933 suggested that the lesions of the pancreas might be due to thickening of acinar secretion; this inspissated material might cause obstruction with resulting hypofunction of the secretory mechanism. Farber[8,9] also advanced the theory that the pan-

creatic secretion is abnormal in fibrocystic disease of the pancreas, and that this causes intrinsic obstruction of the acini and small ducts, finally producing dilatation and obstruction in the larger ducts. He also found inspissation of secretion and dilatation of similar character in the glands of the trachea, bronchi, esophagus, duodenum, gallbladder and intestinal tract, the inspissation of bile perhaps being sufficient to cause intrahepatic biliary obstruction. He suggested that a generalized disorder of secretory mechanism must be present. This involves many glandular structures but exerts its greatest effect on the pancreas. This concept needs further confirmation.

Baggenstoss and Kennedy[3] reported that in their cases the bronchi and their glands usually contained an exudate more purulent than mucoid. Occasionally the bronchial glands were distended with mucus. The only evidence of abnormal glandular secretion, except of these structures and the pancreas, was dilatation and distention of the glands of the duodenum.

Meconium ileus which is grouped with fibrocystic disease of the pancreas was described by Landsteiner[16] in 1905. The term is used to describe an intestinal obstruction in the newborn caused by inability of the intestines to propel through the lumen a thick, mucilaginous meconium, the altered physical state of which is explained by the failure of pancreatic enzymes, particularly trypsin, to act on it during intra-uterine life.[8] Rupture of the intestines and meconium peritonitis may occur. As a rule typical lesions are found in the pancreas at necropsy. There is pancreatic fibrosis with obstruction to the outflow of secretions. This obstruction has been proved in some cases to be due to congenital atresia or stenosis of the main pancreatic ducts. In other instances obstruction is not so obvious and the appearance is suggestive of the changes found in the pancreas of infants who have died of fibrocystic disease of the pancreas. Lesser degrees of intestinal obstruction may be produced by inspissated meconium resulting from stenosis of the ileocecal valve without pancreatic achylia. The condition has been reported as resulting from obstruction to the flow of bile into the intestines without any lesion of the pancreas. Respiratory infection does not occur in these patients, probably because they die so soon after birth. Hurwitt and Arnheim reported the cases of 2 infants who survived for some time after surgical intervention had relieved the intestinal obstruction. Both of these patients died as the result of respiratory infection. Meconium ileus has been reviewed recently by Hurwitt and Arnheim[13] and Kaufmann and Chamberlin.[15]

The current interest in fibrocystic disease of the pancreas is based largely on the independent investigations of the subject by Andersen[1] and Harper[12] in 1938 and Rauch, Litvak and Steiner[23] in 1939. Aided by observations made by earlier investigators supplemented with astute personal observations, these investigators have offered a lucid and coherent concept of fibrocystic disease of the pancreas as a disease entity. Farber[8,9] has contributed much to complete the picture.

Andersen[1] divided the cases of fibrocystic disease of the pancreas into 3 groups: (1) those in which death occurred in the neonatal period; there was intestinal obstruction due to meconium ileus; (2) those in which death occurred between the neonatal period and 6 months of age; the outstanding symptom in these cases was chronic respiratory infection but also there was failure to gain weight and, in some instances, other mild evidences of celiac syndrome; (3) those in which death occurred after the sixth month of age; chronic respiratory infection was present and in most instances the celiac syndrome was obvious.

Not much need be said with regard to patients who have meconium ileus. The outstanding symptoms are those of intestinal obstruction, and death comes rapidly. Neuhauser[21] reported having made the diagnosis of meconium ileus before death by means of roentgenologic methods; this topic will be mentioned later.

The second group described by Andersen is the largest, according to Farber, and includes the cases most difficult to recognize. The symptoms are predominantly those of chronic respiratory infection. Cough which usually is dry and brassy to begin with will persist, perhaps for weeks, and become productive. It frequently simulates the cough of pertussis. Gastro-intestinal symptoms may be moderate or absent. The patient's failure to gain weight may be falsely attributed to the chronic respiratory infection. Steatorrhea may be present but frequently is not obvious grossly and may be overlooked. Since the celiac syndrome often is not obvious, the true nature of the disability frequently escapes recognition until necropsy.

The third group described by Andersen is smaller than the second and usually offers less difficulty in diagnosis. As a rule the celiac syndrome is obvious and this with the associated chronic respiratory infection should suggest fibrocystic disease of the pancreas. The longer the patient survives the more likely that the typical celiac syndrome may be seen.

Fibrocystic disease of the pancreas must be distinguished from idiopathic steatorrhea. As many observers have noted, fibrocystic disease of the pancreas becomes apparent earlier in life. Prolonged chronic respiratory infection is an outstanding feature of this condition, whereas in idiopathic steatorrhea pulmonary infections are found only as an intercurrent infection or a terminal affair. Death in idiopathic steatorrhea is the result of exacerbation of the diarrhea as a rule. Patients who have idiopathic steatorrhea live longer than those who have pancreatic disease. The familial tendency is not found in idiopathic steatorrhea.

If fibrocystic disease of the pancreas is present, the diagnosis can be substantiated by estimating the pancreatic enzymes of the duodenal contents. Their absence or marked diminution (especially trypsin) is almost pathognomonic of the fibrocystic disease when it occurs in patients of this age who have the symptoms described. The fat content of the stools is an aid to diagnosis but this can be deceiving. It is true that in these cases the stools are often grossly fatty but at times this is not so obvious. In Andersen's second group it has been found that steatorrhea may be mild and may not be recognized. Also it must be kept in mind, when analyzing stools for fat, that the fat content of stool specimens of normal infants and children varies from 10 to 80% of dried feces.[8] The ratio of neutral fat to hydrolyzed fat does not serve to distinguish fibrocystic disease from idiopathic steatorrhea, as in the former intestinal lipase is still present.[1,8] Other laboratory tests are of interest but not pathognomonic. Rauch and his associates and Shohl, May and Shwachman have taken the excessive nitrogen in the feces to be an important point in diagnosis. Glucose tolerance tests reveal a low type of curve. Tests for vitamin A absorption show impairment.

Blackfan and May[5] and others have reported that roentgenologic studies in cases of fibrocystic disease of the pancreas show the small bowel pattern suggestive of a deficiency state described by Snell and Camp.[25] This consists of delayed motility and alterations in the mucosal relief of the small intestine, with smoothing of the contours of the lumen, obliteration of the usual markings of the *valvulæ conniventes* and clumping of the barium in

elongated masses. It is true that such an appearance may be obtained in fibrocystic disease but it must be kept in mind that other conditions can produce this picture, and among them idiopathic steatorrhea. Golden[11] stated that before the age of 1 month, and frequently up to 3 or 4 months of age, the normal small bowel pattern is identical with that of a deficiency state in older children. Neuhauser[21] warned that this appearance in infants must not be falsely interpreted as evidence of fibrocystic disease of the pancreas. Thus the roentgenologic examination of the small bowel is of limited value in this condition.

Neuhauser[21] has described the roentgenologic appearance of the abdomen in infants with meconium ileus and by his criteria he has been able to make a correct diagnosis in 4 of the last 10 cases that he has seen. In those cases in which no definite roentgenologic diagnosis could be made, there was only evidence of intestinal obstruction as shown by marked dilatation of loops of small bowel with gas and fluid levels in the small bowel when the patient was in the erect position. This picture simulates that produced by atresia or marked stenosis of the ileum. In those in which the roentgenologic diagnosis of meconium ileus could be made the appearance was different and, according to Neuhauser, typical of that condition. The small bowel was distended without abrupt termination of the visualized gas. Small and minute bubbles of gas could be seen throughout the distal part of the small bowel. These were apparently caused by small quantities of gas being forced into the tenacious mucilaginous meconium. This distal portion of the bowel was somewhat smaller in caliber than that which was well distended with gas. By these criteria more cases of meconium ileus may be diagnosed in the future.

Osteoporosis has been reported rather consistently in fibrocystic disease of the pancreas. It is considered to be due to vitamin D deficiency or lack of calcium or both. It is remarkable that rickets is found so infrequently.

A review of the reported cases of fibrocystic disease of the pancreas revealed that roentgenograms of the thorax have been used frequently to confirm the clinical evidence of respiratory infection. As a rule, however, no detailed report of the roentgenologic appearance of the lungs has been given, it has merely been stated that the roentgenograms revealed pulmonary infection. In view of the prominent part that respiratory infection plays in this disease, it is surprising that more attention has not been paid to the roentgenologic aspect.

Attwood and Sargent[2] in 1942 described pulmonary changes in fibrocystic disease of the pancreas as seen in the roentgenogram. They reported a diffuse pathologic process involving all lobes of both lungs which was most marked at the hilus and decreased in intensity toward the periphery. These roentgenologic changes suggested a chronic or subacute process rather than an acute change. They noted that in contrast to ordinary bronchopneumonia the changes in the upper parts of the lungs were as marked as in the bases. Repeated roentgenographic examinations revealed the chronic character of the pulmonary changes. They found atelectasis in a certain percentage of cases. These pulmonary changes were observed also by Menten and Middleton.[18] Baylin[4] noted also persistent mottling at the bases; a honeycomb-like picture in the lower part of the lungs coupled with linear streaks that followed the bronchial pattern and was suggestive of bronchiectasis.

In 1943 Neuhauser[20] made a careful study of the roentgenograms in cases of this type and again in 1944.[21] He divided the pulmonary changes

into two stages. The first stage is characterized mainly by emphysema and atelectasis, dependent on the partial or complete obstruction of the bronchi or bronchioles. He noted that lobular atelectasis is difficult to distinguish from pneumonic consolidation. Lobar atelectasis is more easily identified. Obstructive emphysema, he found, was not difficult to identify; it produced increased radiolucency of the lung and widening of the interspaces with, perhaps, bulging. In the second stage infection is superimposed. In this stage hilar shadows are accentuated and bronchovascular markings are increased symmetrically. There are multiple areas of peribronchial infiltration which may be confluent and suggestive of pneumonia. Bronchiectasis is often present but he found, as have others, that it is difficult to identify without the use of lipiodol, which is not warranted. The ultimate roentgenologic appearance in a patient with long-standing disease is one of pulmonary emphysema with areas of atelectasis. There is diffuse pulmonary infection consisting of peribronchial pneumonia, bronchiectasis and bronchiectatic abscesses. The changes in the lungs are widespread, involve the apices and bases and extend to the periphery. As a rule there is no pleural reaction.

The pulmonary changes described by Neuhauser have been confirmed by Merner and Bosma.[19] They, too, emphasized the frequency with which emphysema and atelectasis are found associated with widespread pulmonary infection on roentgenologic examination.

Neuhauser's description is outstanding; with his correlation of the roentgenologic aspects of the pulmonary changes with the well-established clinical and pathologic picture. Atelectasis and emphysema with superimposed infection are the usual findings at necropsy. Neuhauser has shown that these changes can be seen in the roentgenogram before death.

As the result of his roentgenologic observations, Neuhauser has said: "It is to be assumed that this appearance is not pathognomonic, but the recognition of a long standing pulmonary disease characterized by obstructive emphysema, atelectasis, fibrosis, and widespread infection involving all lobes is sufficient to warrant a tentative diagnosis of pancreatic fibrosis to be confirmed by examination of the enzyme activity of the duodenal juice." Merner and Bosma also considered the pulmonary changes fairly characteristic and of great assistance in diagnosis. These opinions seem to be warranted. It is expected that this diagnosis will be suggested by roentgenologists more frequently in the future and it is hoped that as a result of this, the antemortem diagnosis will be made with greater accuracy.

In 8 of the last 10 cases of fibrocystic disease of the pancreas seen by Neuhauser, the roentgenologic diagnosis has been correct. Markel[17] reported 1 case in which the diagnosis was first suggested by the roentgenologist. In this case the celiac syndrome was slight and had not been noted until the roentgenograms of the thorax revealed changes which were suggestive of those found associated with fibrocystic disease of the pancreas.

Summary. It may be stated that fibrocystic disease of the pancreas is a disease entity characterized by the celiac syndrome and chronic respiratory infection. There is pancreatic insufficiency and the most important diagnostic procedure is examination of the duodenal contents for evidence of pancreatic achylia. Symptoms of respiratory infection often predominate and roentgenologic examination of the thorax may reveal pulmonary changes that are rather characteristic of this disease. Meconium ileus may be diagnosed, at times by the roentgenologic examination of the abdomen.

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BOOK REVIEWS AND NOTICES

PUBLIC MEDICAL CARE. Principles and Problems. By FRANZ GOLDMANN, M.D. Pp. 226. New York: Columbia Univ. Press, 1945. Price, $2.75.

PUBLIC medical care is defined as being medical care supported by funds obtained by taxation and administered by a governmental agency. The book is written from the point of view that "adequate medical care is a fundamental human right. It is as much a necessity of life as food, shelter, clothing, or education. It is no less indispensable to the well-being of society than to the welfare of the individual." With such a premise, it is inevitable that the extensive study on which this book is based would reveal many inadequacies in the present status of public medical care. In fact, the first and major part of the book entitled "Haphazard Growth," is largely concerned with the existing problems of public medical care, while in each chapter the progress of haphazard growth is traced.

After a short discussion of the pattern of progress, the developments of public medical care are described and analyzed in chapters on the growth of public hospitals, the evolution from the "free dispensary" to the public medical center, the development of programs of public medical care for "persons in need" and the present framework of administration of public medical care.

The second part of the book is entitled "Directed Growth," and is a discussion of the planning for hospitals and related facilities, for the organization of professional services, for the payment for facilities and services and for the administration of medical care, closing with a section on the underlying philosophy of medical care.

The book is an attempt to give a composite picture of public medical care as a social movement. It is written with a background of knowledge of the problems of other countries, as well as of our own, and exhibits a careful and documented study carried on with a broad and comprehensive view of the relation of health to social security and economic welfare.

It is clearly demonstrated that the haphazard growth of medical care that has taken place in this country has resulted in administrative confusion and lacks system or unity, and the conditions have led many who have seriously studied the problems of public medical care to agree that "the house urgently needs rebuilding from bottom up." The book serves a useful and important purpose by bringing into a clear light the present deficiencies of public medical care in relation to the possible value of modern medicine both for the individual and for society as a whole.

In the second part of the book, on planning for medical care, the author has presented sound and forward-looking ideas which conform with those that are now rapidly taking shape in planning a National Health Service as a component of social security. He, therefore, directs attention to the fundamental problems involved in a wide coverage of the population by public medical care, and points out the desirability of centralized control with localized administration in the planning of medical care. This book should be given careful consideration by both laymen and members of the health professions who are called upon to participate in the field of health organization. It is a field in which all intelligent people should have an interest; because, as quoted from Sir Arthur Newholme, "The health of every individual is a social concern and responsibility" as "medical care in its widest sense for every individual is an essential condition of maximum efficiency and happiness in a civilized community."

G. R.

PENICILLIN AND OTHER ANTIBIOTIC AGENTS. By WALLACE E. HERRELL, M.D., M.S., F.A.C.P., Assistant Professor of Medicine, the Mayo Foundation, University of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn. Pp. 348; 45 figs.; 45 tables. Philadelphia: W. B. Saunders, 1945. Price, $5.00.

THIS monograph deals fully with the preparation, properties, and uses of penicillin and similar agents. Published at a time when optimal dosage for the treatment of many diseases is still a matter to be determined, it can be used only as an introduction to therapy, lest one fall into serious error.

W. J.

DIETOTHERAPY. CLINICAL APPLICATION OF MODERN NUTRITION. Edited by MICHAEL G. WOHL, M.D., Associate Professor of Medicine, Temple University School of Medicine; Chairman, Advisory Committee on Nutrition, Philadelphia Department of Public Health. Pp. 1029; 92 figs., numerous tables and charts. Philadelphia, W. B. Saunders, 1945. Price, $10.00.

A BOOK as inclusive as this one can be recommended as a source of ready reference. The importance of various elements of diet is considered fully in relation to normal nutrition, periods of "physiologic stress," and many medical and surgical disorders. The 44 sections have been written by 58 contributors. The material is well organized, and is enhanced by an adequate index and bibliography. The reader might even be warned against becoming engrossed to the extent that he forget therapeutic measures other than food and vitamins.

W. J.

TRAUMA IN INTERNAL DISEASES. By RUDOLPH A. STERN, M.D., Asst. Attending Physician, City Hospital, New York, N. Y. Pp. 590. New York: Grune & Stratton, 1945. Price, $6.75.

THE part that trauma may play in causing or aggravating internal diseases is always a perplexing problem. Legal aspects of these questions, often scientifically insoluble, must be decided by the courts; however, that justice may be best served, it is important that all facts be readily available. Dr. Stern's book is a critical compilation of important case histories and experimental work bearing on these diseases. As such it helps fill a gap in the literature in English.

In the introduction the author discusses the problems and common errors of rendering testimony in medico-legal cases. Then follows a systematic recital of various diseases, with abundant documentation from the medical and legal literature. The examples used are chosen either because they carry weight as scientific evidence or because they demonstrate the courts' demonstrated attitude in such cases.

There is a good bibliography. The printing is good but the quality of paper and binding show the effect of wartime shortages.

This book will be most useful to practitioners who must give evidence and express expert opinion in the courts and to lawyers who deal with such cases.

W. S.

EFFECTIVE LIVING. By C. E. TURNER, A.M., ED.M., SC.D., DR.P.H., Professor of Public Health, Massachusetts Institute of Technology; formerly Assoc. Professor of Hygiene, Tufts Medical and Dental Schools; and ELIZABETH MCHOSE, B.S., M.A., Director of Physical Education for Girls and Chairman of the Health Council, Senior High School, Reading, Pa. Second Ed. Pp. 432; 164 ills. St. Louis: Mosby, 1945. Price, $2.00.

THE authors' aim is to help youth discover ways of effective living, which they interpret as the development of one's maximum capacity as an individual, as a member of the family group, and as a useful citizen. Much factual material is included in simple terms which are rendered still more comprehensible by a full Glossary. Any youth who has sympathetically studied and assimilated the wisdom in these 400 small pages will necessarily be greatly aided toward the triple goal. Most of us would scoff, however, at the hope of

getting any number of youth to do just this, were it not for the experiences of the authors in the class room and the success that they seem to have met in at least 2 high schools. Caveat criticus! E. K.

THE HUMAN BODY. By LOGAN CLENDENING, M.D., Professor of Clinical Medicine, University of Kansas. Fourth Ed. Pp. 443; 106 figs. New York: Alfred A. Knopf, 1945. Price, $4.00.

THIS little book remains a readable introduction to medicine for the laity. It contains some misstatements of fact, however, and might be criticized by voracious readers of the news magazines as being a little out of date. W. J.

THE STORY OF A COUNTRY MEDICAL COLLEGE. A History of the Clinical School of Medicine and The Vermont Medical College, Woodstock, Vt., 1827–1856. By FREDERICK CLAYTON WAITE. Pp. 213. Montpelier, Vt.: Vermont Historical Society, 1945. Price, $4.50.

As the author points out, the major importance of this book is that it is the first history of a country medical college to be published. They had characteristics quite different from those of urban medical colleges. One third of all the medical colleges founded before the Civil War were country medical colleges and not far from one-third of all the men who attended any medical college before 1861 went to a country medical college. For Vermonters it has the added local interest of details (including a catalogue of faculty and students) about one of the state's influential educational institutions, successful in its day but "almost forgotten in the 88 years since it closed." We read of the College's foundation by Dr. Joseph A. Gallup in 1827, of his frustration by younger associates leading to his resignation after 8 years, of its temporary affiliations with 2 colleges of Arts (Waterville, Middlebury), of its 18 years of independent existence, and 20 years of coöperation with another school, of such items as the difficulties in teaching anatomy, and dissensions in the faculty, that have a familiar ring for the larger as well as the smaller schools. French methods of physical diagnosis were brought to the Vermont Medical College by Alonzo Clark in 1842, experimental mammalian physiology (gastric fistulas in dogs *au Beaumont*) by J. C. Dalton, Jr., in the fifties. But medical education was already concentrating in the larger centers where clinical instruction was available and in 1857 decreasing attendance caused the resignation of the faculty and brought an end to our story.

The author has performed a "labor of love" satisfactorily, as was to be expected from his well-rounded education and previous historico-literary activities and affiliations. E. K.

THE HISTORY OF SURGICAL ANESTHESIA. By THOMAS E. KEYS. With an Introductory Essay by CHAUNCEY D. LEAKE, and a concluding chapter, The Future of Anæsthesia, by NOEL A. GILLESPIE. Pp. 191. New York: Schuman's, 1945. Price, $6.00.

DR. KEYS appropriately begins his admirable special history with an illustration from the Nuremberg Chronicle of the first recorded anesthesia—the "deep sleep" that fell upon Adam when Eve was brought forth from his side. From then on, the same entertaining point of view carries us, both pleasantly and authoritatively, rapidly through the early stages (28 pages from "the beginnings" to Morton), with the bulk of the text devoted to the last 100 years. The 16 parts of Section I deal separately with a number of general and local anesthetics, "twilight sleep," anoci-association, various modes of administration (rectal, caudal, intravenous, endotracheal, etc.), apparatus, and physiologic and pharmacologic factors. One of the most praiseworthy features of the book, a feature which indeed sets a high standard for other special subject histories to emulate, is the rich bibliography offered in quadruple form (references for Section I, a chronologic list, a list by subject, then by author) which greatly increases its value for those seeking sources in

this field. The 77 pages that they occupy are well spent, even in these days of paper shortage, and testify to the painstaking scholarly nature of the whole volume. The interesting personalized Introductory Essay by Leake—himself a distinguished maker of anesthesia history—together with N. A. Gillespie's comments on The Future of Anesthesia, and Fulton's Appendix on the Morton and Warren Tracts on Ether (Letheon) add still further to the value and interest of this excellent production. The Reviewer wishes to add a final word on the advantages accruing from the excellent qualifications of those who contributed to the contents of the book and from their easy access to the greatest of medical libraries. E. K.

THE AVITAMINOSES. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Emeritus Professor of Physiological Chemistry, Teachers College, Columbia Univ.; and GILBERT DALLDORF, M.D., Pathologist of the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y.: Third Ed. Pp. 438; numerous plates and tables. Baltimore: Williams & Wilkins, 1944. Price, $4.50.

THIS well-known treatise on the avitaminoses is now in its 3rd edition. It has been carefully revised; the chapter on the mode of behavior of the vitamins has been rewritten. The chemistry and nature of the individual vitamins, the pathology of experimental avitaminoses and of the clinical deficiencies is presented in detail. An excellent bibliography is appended. Tables of the vitamin values of foods and laboratory tests for the recognition of deficiency states are also included. E. W.

ANNUAL REVIEW OF BIOCHEMISTRY, Vol. 14. Edited by JAMES MURRY LUCK and JAMES H. C. SMITH. Pp. 856. California: Annual Reviews, Inc., Stanford Univ. P. O., 1945. Price, $5.00.

THE new 14th volume of the "Annual Review of Biochemistry" maintains the high standard of its predecessors in this review series, which has become invaluable to all interested in biochemical advances. This is the last of the so-called "war" volumes, and, in spite of obstacles which certain reviewers experienced in securing literature from distant sources, it is the largest volume thus far published.

There are 28 individual reviews by experts in the chosen fields. Such topics, commonly reviewed as Biological Oxidations and Reductions, The Chemistry of Carbohydrates, Lipids, Amino Acids and Proteins, and the Metabolism of these constituents (reviewed separately), are once again covered.

Reviews upon more unusual topics are by J. M. Gulland and colleagues (nucleic acids and nucleoproteins), I. Fankuchen (an excellent review on *x*-ray studies of compounds of biochemical interest), C. R. Noller (the triterpenes), W. L. Ruigh (steroids), W. T. Salter (hormones), J. P. Greenstein (biochemistry of malignant tissues), and J. H. Mueller and A. E. Oxford respectively on the timely subjects of The Chemistry and Metabolism of Bacteria, and The Chemistry of Antibiotic Substances other than Penicillin. D. D.

COLLOID CHEMISTRY. Theoretical and Applied. Edited by JEROME ALEXANDER. Pp. 1256; numerous figs. and tables. New York: Reinhold Pub. Co., 1944. Price, $20.00.

THIS volume, which is the 5th in the series, is arranged in 2 sections, the 1st dealing with the theory and methods of colloid chemistry, the 2nd with its applications to biology and medicine. There are included some 60 essays varying in length from 5 to 90 pages, each dealing with the present status of, and recent developments in each special field.

In the 1st section are contained 25 authoritative articles by such experts

as Harkins (on surface films), McBain (on soaps and detergents), Germer (on applications of electron diffraction), Huggins (on *x*-ray analysis), Hickman (high-vacuum distillation), Mark (polymerization), MacInnes and Longworth (electrophoresis of proteins and related substances), and Pickels (high speed centrifugation). Other topics deal with microradiography of colloidal materials, the electron microscope, elasticity of rubber and similar materials, the vitreous state, sonic and ultrasonic waves in colloid chemistry, the cyclotron and betatron, selective adsorption, and numerous other topics.

In the biologic field excellent articles are presented by Astbury (proteins), Rothemund (photosynthesis), Farr (plant cell membranes), Hixon and Rundle (advances in starch chemistry), Axelrod and Elvehjem (enzymes and biological action of vitamins), Lauffer and Stanley (colloid chemistry of purified viruses), Barth (colloid chemistry of embryonic development), Chambers (physical properties of protoplasm), Meyerhof (physical changes in muscular activity), Landis (the capillary circulation), Menkin (inflammation), Boyd (immunology), Cannon (homeostasis), Loeb (cancer), and Carlson (gerontology). This list is incomplete but represents a fair cross-section of the material covered in this huge volume. Undoubtedly other articles will appeal to different readers.

It is perhaps unfortunate that this single volume encompasses such a wide range of topics. Nearly every scientist will find some of these articles stimulating, but it seems hardly likely that many will be sufficiently interested in all or most of these topics to purchase such an expensive volume. The editor has, however, contributed a distinct service. Here in excellently presented form is an authoritative discussion and correlation of the fundamental phenomena of colloid chemistry and biology. S. G.

THE ABORTION PROBLEM. Proceedings of the Conference held under the auspices of the National Committee on Maternal Health, June 1942. HOWARD C. TAYLOR, JR., M.D., Conference Chairman. Pp. 182. Published for the National Committee on Maternal Health. Baltimore: Williams & Wilkins, 1944. Price $2.50.

THIS volume deals with the magnitude of the abortion problem, spontaneous abortion and its prevention, the social, moral and economic causes and control of abortion, and a summary and the recommendations of the conference. There are between 3000 and 4000 deaths a year in this country due to abortion, and the death rate from this cause appears to be changing very little if at all. About 30% of maternal deaths are due to this cause.

The papers and the discussions forming the substance of this volume are excellent and make interesting and instructive reading. The recommendations are conservative and sound. The volume is recommended to all who are interested in the problem of abortion. D. M.

DISEASES OF THE BREAST. By CHARLES F. GESCHICKTER, M.A., M.D., LT. COMDR., MC, USNR, Director of The Francis P. Garvan Cancer Research Laboratory; Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School. Second Ed. Pp. 826; 593 ills. Phila.: Lippincott, 1945. Price, $12.00.

THIS 2nd edition represents a considerable expansion of the original volume. The section dealing with mammary carcinoma has been brought up to date and enlarged. The chapter on the Mechanism of Tumor Formation has been entirely rewritten. New material includes the use of penicillin for infectious mastitis, endocrine therapy in chronic cystic mastitis, the criteria of operability and inoperability of mammary carcinoma.

In the chapter on The Mechanism of Tumor Formation, the author dwells entirely upon the rôle of estrogenic hormones, stating that ". . . the sequence of estrogenic response on the part of the mammary gland may be

considered as highly significant. The changes leading up to cancer may be looked upon as essential steps in the cancer process and as forming a definite pattern for the development of malignancy in any tissue, regardless of the means employed to induce it. In the belief that the latter interpretation is correct, the sequence of estrogenic effects will now be summarized etc." Whereas this concept is acceptable as a working hypothesis, more especially in regard to breast tumors, its wholehearted acceptance must await confirmation. At present many investigators of neoplastic processes would regard such a stand as untenable.

The volume is conveniently arranged, well illustrated, and readable. It contains a wealth of material for the clinician, surgeon and pathologist; a valuable addition to anyone's medical library. D. C.

THEORY OF OCCUPATIONAL THERAPY. By NORAH A. HAWORTH, M.A. (CANTAB.), M.R.C.S., L.R.C.P., D.P.M., Assistant Medical Officer, London Passenger Transport Board; late Medical Officer, Horton Emergency Hospital; and Senior Assistant Medical Officer, Severalls Mental Hospital, Colchester; and E. MARY MACDONALD, Prin., Dorset House School of Occupational Therapy, Barnsley Hall Emergency Hospital, Bromsgrove; Member of the Association of Occupational Therapists. Second Ed. Pp. 148; 68 figs. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

THIS book gives a fairly good general picture of all phases of occupational therapy. It would be, in the opinion of the Reviewer, instructive for those who are little acquainted with the work; but to those in the field it presents nothing more than a neat compilation of facts already known. Another criticism is that it does not treat adequately the needs of the present-day program in a military hospital, at least, in this country. New crafts and new theories are being worked out in these hospitals every day; yet, little mention is made of them

In the chapters describing the adaptation of equipment for specific treatment, many excellent ideas are given; but it seems to the Reviewer that such a complete change of the machinery would make occupational therapy so bizarre that it might well produce a poor psychologic effect on the patient.

C. W.

SEGMENTAL NEURALGIA IN PAINFUL SYNDROMES. By BERNARD JUDOVICH, B.S., M.D., Instructor in Neurology, Graduate School of Medicine, University of Pennsylvania; Clinical Instructor in Neurology, Women's Medical College; Chief of Neuralgia Clinics, Philadelphia General Hospital, Graduate Hospital, and Women's Medical College Hospital; and WILLIAM BATES, B.S., M.D., F.A.C.S., F.I.C.S., Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Consulting Surgeon, Babies' Hospital and Philadelphia Home for Incurables; Consulting General Surgeon, Wills Hospital, Phila. Pp. 313; 178 ills. Phila.: Davis, 1944. Price, $5.00.

THIS monograph develops a single theme, simply, effectively and forcefully. The interpretation of pain is a task of every physician whether specialist or general practitioner, and the authors present observations which should help physicians in this task. As stated in the Preface, "the interpretation of pain can be greatly facilitated by eliciting hyperalgesic or tender skin zones. The combination of segmental pain and tenderness appears to be due to factors which irritate roots, ganglia, or trunks of the spinal sensory nerves, and not due to painful impulses originating in diseased viscera."

Whether or not this thesis is correct, it demands the attention of neurologists, neurosurgeons, and anesthesiologists, all of whom are directly concerned with the relief of pain. It can also be read profitably by the average physician, since diagnostic as well as practical therapeutic suggestions are offered in detail.

For a volume published in wartime the paper, type and illustrations are satisfactory. They do not compare, however, with pre-war standards.

R. D.

THE CHEMICAL FORMULARY. A Collection of Valuable, Timely, Practical Commercial Formulæ and Recipes for Making Thousands of Products in Many Fields of Industry, Vol. VII. Editor-in-Chief, H. BENNETT. Pp. 474. Brooklyn: Chemical Publishing Co., 1945. Price, $6.00.

THIS volume, the 7th in the series, contains more than 2000 formulas for mixing and making products ranging from adhesives to rust preventatives and from cold creams to roach killers. Farmers, both amateur and professional, will find here directions for preparing insecticides, fertilizers and livestock medicines at low cost. There is useful information for the photographer, painter, chemist, as well as the housewife. Material covered here includes adhesives, flavors and beverages, cosmetic and drug products, emulsions and colloids, farm and garden specialties, food products, inks, leather, lubricants and oils, construction materials, metals and alloys, paint, varnish and lacquers, paper, photography, polishes, explosives, plasters, resins, rubber, wax, soaps and cleaners, textiles as well as a number of miscellaneous articles.

The directions for using the formulas are simple and direct, as this volume, in contrast to previous volumes, has been written for laymen. This work will be a storehouse of information to persons in all walks of life. S. G.

AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS. By Various Writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (OXON.), F.R.C.P., Consulting Physician Guy's Hospital; late Physician, H.M. Household. Assisted by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Physician, Guy's Hospital; Honorary Physician, All Saints' Hospital for Genito-urinary Diseases. Pp. 1128; 798 ills. of which 231 are colored. Sixth Ed. Baltimore: Williams & Wilkins Co., 1945.

THIS book offers a ready reference on the application of differential diagnosis to all the main signs and symptoms of disease. All symptoms and signs that are encountered on the examination of a patient are adequately listed, and a short note about various disease complexes in which they may occur are discussed briefly and concisely. This edition has only a few changes from the fifth. The number of colored plates has been increased and several sections rewritten. More note is also given to that group of disease that has gained added importance because of the war. J. F.

PSYCHIATRY IN MODERN WARFARE. By EDWARD A. STRECKER, A.M., M.D., LITT.D., LL.D., Professor of Psychiatry, School of Medicine, University of Pennsylvania; Consultant to the Surgeon-Generals of the Army and the Army Air Forces, the Navy and the U. S. P. H. S.; and KENNETH E. APPEL, PH.D., M.D., SC.D., Assistant Professor of Psychiatry and Chief of Clinic, School of Medicine, University of Pennsylvania; Lecturer in Psychiatry, School of Neuropsychiatry, U. S. Naval Hospital, Philadelphia; etc. Pp. 88. New York: Macmillan, 1945. Price, $1.50.

AT a recent meeting, a summary of a comparative study of the two World Wars was so generously received that copies were requested, and the authors now offer this brief treatise. Part I contains Psychiatry and the Two World Wars: Contrasts in the Nature of Warfare; Organization of Neuropsychiatry; Psychological Effects on Civilians; Statistics; Etiology; Symptomatology; Psychopathology; Treatment; Prognosis; The Increase in Psychiatric Conditions. Part II covers Demobilization and the Return to Civilian Life: The Civilian Shares Responsibility for Readjustment; Every Soldier Has a Readjustment Problem; The Philosophy of Helping; Methods of Helping Returning Service Men; Improved Veteran Facilities Imperative.

World War II was global in extent, with new engines of war and methods of destruction. Robot bombs and communication through electromagnetic waves are sent from and received by portable apparatus. Danger at the rear as well as at the front is now great, and civilian populations are a part of the conflict. Increase in the surprise element causes greater fear. The belief that

the lessons of the previous war would decrease the number of neuroses was not substantiated—psychiatrists, the military and people all being responsible. Hypno-narco-analysis is employed. Evipan is used to penetrate amnesias, evipan and pentothal for narcoanalysis. "Group therapy removes the feeling of isolation, minimizes the feelings of queerness, difference, etc. . . ." Preventive psychiatry is successfully employed. It is emphasized that the "*vast majority of military neuropsychiatric diagnoses do* (sic) *not signify an incapacity to become an effective worker.*" Psychiatric conditions are now so common that "one-third of the physicians in the country should be psychiatrists or able to treat psychiatric conditions intelligently." N. Y.

TEXTBOOK OF ANÆSTHETICS. By R. J. MINNITT, Trinity College, Cambridge, M.D. (Liverpool), D.A. (R.C.P. & S. Eng.) Lecturer in Anæsthesia, University of Liverpool, and JOHN GILLIES, M.C., M.B., CH.B. (Edinburgh), D.A. (R.C.P. & S. Eng.) Consultant in Anæsthetics, Department of Health for Scotland. With a chapter on Local and Regional Analgesia by L. B. WEVILL, M.B., F.R.C.S. (Ed.), Major R.A.M.C. Sixth Ed. Pp. 487; 199 figs. Baltimore: Williams & Wilkins Co., 1944. Price, $7.00.

THIS is a completely revised and considerably enlarged version of the "Handbook of Anesthetics" originally written by Ross and Fairlie. The new authors, who are eminently qualified for their task, have undertaken it in much the same fashion as other British anesthesiologists. Thus, there is emphasis on technique, apparatus and minutiæ, with less attention to broad principles and fundamental background. Furthermore, the volume represents the English devotion to inhalation anesthesia as contrasted to other well accepted methods of pain relief. Spinal anesthesia, for example, receives but 20 pages in the 487 page book.

A textbook on anesthesia is difficult to write, for there is a small group of qualified physicians, specializing in the field, and a large group who "dabble." The former are concerned with establishing their field on a sound scientific foundation and this type of work is of only passing interest. The latter need guidance and direction. For them this work is primarily intended. It is simple and didactic.

New chapters on trichlorethylene, endotracheal anesthesia, intravenous anesthesia and anesthesia for dentistry have been included. A new chapter on choice of anesthetic is well done.

The book should be read with full realization of its limitations, *i. e.*, a national rather than international outlook, together with a somewhat oversimplified approach. R. D.

PULMONARY TUBERCULOSIS IN THE ADULT. Its Fundamental Aspects. By MAX PINNER, M.D., Chief, Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York; Editor, American Review of Tuberculosis; Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York. Pp. 579. Springfield, Ill.: Charles C Thomas, 1945. Price, $7.50.

THIS book is a highly valuable contribution to the fundamental understanding of adult pulmonary tuberculosis, its prevention and treatment. Unlike other books addressed to clinicians it presents the essential, pertinent, scientific data on the pathogenesis of the disease in an adequate and integrated manner—a subject which is often dismissed perfunctorily—so that the clinician is left in a scientific desert as far as the practice of the specialty is concerned. The first part of the book is devoted to a consideration of the fundamental aspects of the tubercle bacillus, the histogenesis of the lesions as they occur in man, the rôle of tuberculin, the principles of immune reactions and the factors which control the progression and healing of pulmonary phthisis. While these data have been discussed in other books at greater length, the latter stress animal experimentation and give but scant attention to the practical problems of the human disease. It is true that Dr. Pinner, in presenting

this self-consistent interpretation of the disease as a whole, often expresses personal opinions; they are, however, properly labeled and not introduced with the assumed halo of an *ex cathedra* oracle. On the contrary, attached to each chapter are citations from the literature which give contrary views. This bibliography has the novel and useful advantage in that it appends to each citation a concise statement of the essential nature of the contribution and its evaluation. Then follows a more direct consideration of the primary complex and tuberculosis in children, the classification of pulmonary tuberculosis, where it is stressed that, in evaluation of prognosis, it is not the extent of the disease which is significant, but rather the inherent aptitudes of progression and regression which characterizes the lesion. Excellent Roentgen ray and autopsy photographs illustrate and clarify the text. Special chapters are devoted to tracheobronchitis, diagnostic principles, laboratory procedures and the physiology of respiration and pulmonary collapse. Guides to medical treatment are given in the light of the data on the pathogenesis of the disease previously recorded. The last chapter considers its epidemiology in a penetrating manner.

This book is highly recommended to every clinician as an integration of present knowledge derived not only from American sources. It is restrained in its conclusions and sound in its judgment and appears to me the most acceptable and philosophically integrated book on the subject. M. L.

THE ART OF RESUSCITATION. By PALUEL J. FLAGG, M.D., Chairman, Comm. on Asphyxia, Am. Med. Assn.; President and Founder of the Soc. for the Prevention of Asphyxial Death, Inc.; Visiting Anæsthetist, Manhattan Eye and Ear Hospital; Consulting Anæsthetist to St. Vincent's (and other) Hospitals. Pp. 453; 176 figs. N. Y.: Reinhold, 1944. Price, $5.00.

THERE can be no doubt of the contributions of the author in fixing attention on the hazards of asphyxia long before the medical profession as a whole was aware of these hazards. In recent years, instead of strengthening his position by research and fundamental observations, Flagg has continued to devote his energies to the printed word. This book is the logical outcome of such a career. It represents an extremely important viewpoint without scientific documentation. It is of great interest historically; of less value to the individual challenged by the fundamental problems of resuscitation. Its title is essentially correct representing "The Art"—rather than "The Science of Resuscitation."

In fairness to the author it should be pointed out that his purpose is clearly stated in the preface, "The matter presented herein is elementary. It presents a framework upon which the experiences and the contacts of the author may readily be studied. Should this form and matter prove of interest, the entire subject, it is hoped, will attract the attention and enlist the activities of highly qualified research workers and technicians."

The reviewer recommends this book to physiologists and anesthesiologists, primarily because of its historical importance. It is not recommended to the general reader. R. D.

MODERN METHODS OF AMPUTATION. By EDMUNDO VASCONCELOS, Professor, University of São Paulo. With an Introductory Survey of The Development of Amputation by MAJOR GEN. NORMAN T. KIRK, M.C., Surgeon General, U. S. Army. Pp. 253; 258 figs. New York: The Philosophical Library of New York, 1945. Price, $10.00.

THE book, as Dr. Vasconcelos states, was written for the practitioner and not for the expert. However, the author's 20 years of experience has enabled him to present the material in such a clear and understandable manner that the expert as well as the practitioner can benefit by his presentation of the subject. The technics for the various amputations are discussed in detail with

emphasis on the common mistakes that surgeons may make. Only procedures judged by the author to be of clinical value are included in the volume. The illustrations of technics and levels of amputations are vividly illustrated.

H. Z.

FUNDAMENTALS OF ANESTHESIA. An Outline. By Subcommittee on Anesthesia of Division of Medical Sciences, National Research Council. Second Ed. Pp. 231; 81 figs.; 19 tables. Illinois: American Medical Assn. Press, 1944. Price, $2.50.

THIS is an extremely useful manual on practical anesthesia. Although dogmatic and "stream-lined" in its form, the volume is better than any other on the subject. In this new edition the only additions are extra pages on local and spinal anesthesia, together with 9 new illustrations. R. D.

SURGERY OF THE HAND. By STERLING BUNNELL, M.D., Honorary Member of American Academy of Orthopedic Surgeons, Member of American Association of Plastic Surgeons, and of American Society of Plastic and Reconstructive Surgery, Licentiate of American Board of General Surgery and Plastic Surgery. Pp. 734; 597 ills. Philadelphia: J. B. Lippincott, 1944. Price, $12.00.

DR. BUNNELL'S excellent compilation is one which should be available to and should be studied by every surgeon who deals with any condition of the hand. Its comprehensiveness and detail make it superior to previous treatises on the subject. The first of 4 sections covers developmental, comparative and normal anatomy; the second is a detailed discussion of the healing of tissues and the principles of surgical reconstruction of skin, bones, joints, nerves and tendons. Fractures, dislocations, infections and burns are treated in the third section. The last section deals with congenital deformities, tumors, vasomotor and trophic conditions. The book is a valuable addition to medical literature.

H. Z.

NITROUS OXIDE-OXYGEN ANESTHESIA. By F. W. CLEMENT, Major, M.C. (A.U.S.). Formerly Director of Anesthesia at Flower Hospital, The State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent's Hospitals, Toledo, Ohio. Second Ed. Pp. 288; 92 engravings. Philadelphia: Lea & Febiger, 1945. Price, $4.50.

THIS second edition of a well-known little book still represents a single viewpoint—that of the McKesson school. As such, it continues to be of interest to pharmacologists and anesthesiologists.

As the author states "in this revised edition, the changes are those of detail, rather than alterations, of the original concept of the text." Among the new or revised topics are the more detailed method of administration, the dangers of prolonged anoxia, the mechanism and treatment of shock, the rôle of carbon dioxide and that of the sino-aortic areas in anoxia.

Although many experts are not in agreement with the McKesson-Clement theory of nitrous oxide, this monograph forms a valuable addition to any anesthesia reference list. It is not recommended for the novice. R. D.

MEDICAL CLINICS OF NORTH AMERICA. July, 1945. Mayo Clinic Number. Symposium on Medical Emergencies. Pp. 1067; 160 figs. Phila.: Saunders, 1945. Price, $16.00.

OF the two symposia in this number, the first covers the treatment of medical emergencies. This title is rather misleading as neurological, dermatological and obstetrical emergencies are also covered.

The other symposium is on subjects of useful and timely interest. Stilwell's clinic on "Post War Aspects of Some Tropical Diseases" was interesting and

instructive. This article "takes the scare" out of the newspaper articles which would have malaria, filariasis and other tropical diseases reaching epidemic proportions with the return of the infected service man. The clinic on Liver Function Tests by J. F. Weir helps untangle some problems of the interpretation of these tests that face the general practitioner. As usual, this issue of "The Clinics" is a worthwhile addition to medical literature. J. F.

DISEASES OF THE NERVOUS SYSTEM. Described for Practitioners and Students. By F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. (LONDON), Hon. D.Sc., Nat. Univ. Ireland, Physician in charge of the Neurological Dept., University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square. Fourth Ed. Pp. 360. Baltimore; Williams & Wilkins, 1945. Price, $4.50.

THIS remains an excellent textbook of Neurology. Dr. Walshe's style and terse description stimulates the reader to continue on and on. As admitted in the preface, condensation of the field is difficult and readers would vary in criticizing the omissions. For example, Pancoast tumor in the differential diagnosis of cervical rib and group psychotherapy in psychoneurosis were outstanding omissions to me. The exceptionally good chapters were those on the Parkinson syndrome and cerebral hemorrhage and thrombosis. The attitude toward the treatment of neurological diseases would be well worth teaching to every medical man. J. T.

STUDENT'S GUIDE IN NURSING ARTS. By M. ESTHER MCCLAIN, R.N., B.S., M.S., Assistant Professor in Nursing Education, and Instructor in Nursing Arts of the Providence Division of the School of Nursing Education, The Catholic University of America, Washington, D. C. Pp. 407. St. Louis: Mosby, 1945. Price, $3.00.

THIS loose-leaf guide presents the outline in Nursing Arts as taught in a school of nursing education. Each unit and its individual lessons are introduced with concise objectives. There are excellent references to textbooks on nursing arts for each lesson. Review questions on each unit are placed at the end of the unit as a study help. Space is provided throughout the outline for adding notes. Many of the questions are directed to the techniques used in this particular School of Nursing. Therefore, they do not have meaning elsewhere. The titles of the units are the same as those of the outline in the Course Introduction to Nursing Arts as given in the Curriculum Guide for Schools of Nursing. Because of this and the well systematized table of contents, the guide should prove a useful manual not only to students but to instructors as well. L. S.

NEW BOOKS

Trauma of the Central Nervous System. Proceedings of the Association for Research in Nervous and Mental Disease, December 17 and 18, 1943, New York. Pp. 679; 243 illus. and 44 tables. Baltimore: Williams & Wilkins, 1945. Price, $8.00.

Essentials of Clinical Allergy. By SAMUEL J. TAUB, M.D., Professor of Medicine, Cook County Graduate School of Medicine, Fellow of the American Academy of Allergy, formerly Assistant Professor of Medicine, Rush Medical College, of the University of Chicago. Pp. 198. Baltimore: Williams & Wilkins, 1945. Price, $3.00.

Fundamental Principles of Physical Chemistry. By CARL F. PRUTTON, Ph.D., Professor of Chemistry and Chemical Engineering, Case School of Applied Science and SAMUEL H. MARON, Ph.D., Associate Professor of Physical Chemistry, Case School of Applied Science. Pp. 780. New York: Macmillan, 1944. Price, $4.50.

Human Biochemistry. By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Physiology, New York Medical College, Flower and Fifth Ave. Hospitals; Formerly Associate, The Rockefeller Institute for Medical Research, New York. Pp. 573; 70 illus., 5 color plates. St. Louis: C. V. Mosby, 1945. Price, $6.00.

Pulmonary Tuberculosis. A Handbook for Students and Practitioners. By R. Y. KEERS, M.D. (EDIN.), F.R.F.P.S. (GLAS.), Senior Physician and Medical Supt., Tor-na-Dee Sanatorium; Late Assistant Medical Supt., The British Sanatorium, Montana, Switzerland and B. G. RIGDEN, M.R.C.S. (ENG.), L.R.C.P. (LOND.), First Assistant Medical Officer, Tor-na-Dee Sanatorium. Pp. 273; 124 figs. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

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One Hundred Years of Gynæcology (1800–1900). A Comprehensive Review of the Specialty During Its Greatest Century with Summaries and Case Reports of All Disease Pertaining to Women. By JAMES V. RICCI, A.B., M.D., Clinical Professor of Gynæcology and Obstetrics, New York Medical College, Director of Gynæcology of the City Hospital, New York. Pp. 651. Philadelphia: Blakiston, 1945.

Pediatric X-ray Diagnosis. A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology. By JOHN CAFFEY, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, Associate Pediatrician and Roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City. Pp. 838; 710 figs. Chicago: Year Book Publishers, 1945. Price, $12.50.

Facial and Body Prosthesis. By CARL DAME CLARKE, Ph.D., Associate Professor of Art as Applied to Medicine, School of Medicine, University of Maryland; Capt., Sanitary Corps, A.U.S., Dept. of Moulage and Prosthetics, Army Medical Museum. Pp. 200; 75 illus. St. Louis: C. V. Mosby, 1945. Price, $5.00.

Science and the Planned State. By JOHN R. BAKER, M.A., D.Phil., D.Sc. Pp. 120. New York: Macmillan, 1945. Price, $1.75.

American Pharmacy. Fundamental Principles and Practices. By RUFUS A. LYMAN, M.D., Editor-in-Chief; Dean, College of Pharmacy, Director, Student Health Service, University of Nebraska, Editor, American Journal of Pharmaceutical Education. Pp. 540; 197 illus. Philadelphia: J. B. Lippincott, 1945. Price, $8.00.

NEW EDITIONS

A Handbook for Dissectors. By J. C. BOILEAU GRANT, Professor of Anatomy, University of Toronto and H. A. CATES, Associate Professor of Anatomy, University of Toronto. Second Ed. Pp. 390. Baltimore: Williams & Wilkins, 1945. Price, $2.50.

Diseases of the Nervous System. Described for Practitioners and Students. By F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. (LOND.), Hon. D.Sc., Nat. Univ. Ireland, Physician in charge of the Neurological Dept., University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square. Fourth Ed. Pp. 360. Baltimore: Williams & Wilkins, 1945. Price, $4.50.

Recent Advances in Neurology and Neuropsychiatry. By W. RUSSELL BRAIN, M.A., D.M., (OXON.), F.R.C.P., Physician to the London Hospital and the Maida Vale Hospital for Nervous Diseases, etc., and E. B. STRAUSS, M.A., D.M. (OXON.), F.R.C.P., Physician for Psychological Medicine, St. Bartholomew's Hospital. Fifth Ed. Pp. 363; 32 illus. Philadelphia: Blakiston, 1945. Price, $5.00.

Handbook of Physiology and Biochemistry. By R. J. S. McDowall, M.D., D.Sc., M.R.C.P., Professor of Physiology, University of London, King's College. Thirty-eighth Ed. Pp. 898; 305 figs. Philadelphia: Blakiston, 1944. Price, $6.00.

Synopsis of Genitourinary Diseases. By Austin I. Dodson, M.D., F.A.C.S., Richmond, Virginia, Professor of Genitourinary Surgery, Medical College of Virginia. Fourth Ed. Pp. 313; 112 illus. St. Louis: C. V. Mosby, 1945. Price, $3.50.

Textbook of Obstetrics. Designed for the Use of Students and Practitioners. By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College, Obstetrician and Gynecologist-in-Chief, New York Hospital and Director of the Lying-in Hospital, New York City. Third Revision. Pp. 1287; 973 illus. New York: D. Appleton-Century, 1945. Price, $10.00.

A Text-book of Pharmacognosy. By George Edward Trease, B. Pharm., Ph.C., F.R.I.C., F.L.S., Lecturer on Pharmacognosy and Acting Head of the School of Pharmacy in the University College of Nottingham. Fourth Ed. Pp. 799; 268 figs. Baltimore: Williams & Wilkins, 1945. Price, $7.50.

CORRECTION

We regret that the following article was omitted from the Table of Contents in the October issue:

Use of a Simple Postural Test in Neurocirculatory Asthenia 511
By Major William A. Jeffers, M.C., A.U.S., Capt. Samuel C. Sheiman, M.C., A.U.S., and Lt. Col. George H. O'Brasky, M.C., A.U.S.

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